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Original Research

Update on familial hypercholesterolemia: An expert clinical consensus from the National Lipid Association

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Familial hypercholesterolemia (FH) is a common genetic disorder characterized by lifelong elevated low-density lipoprotein cholesterol (LDL-C), leading to a high risk of early onset atherosclerotic cardiovascular disease (ASCVD). This document provides an update to the National Lipid Association's 2011 clinical guidance, summarizing the remarkable progress in the field. With a global prevalence of approximately 1 in 311, FH remains severely underdiagnosed. This guidance reviews current diagnostic criteria, including the expanding role of genetic testing to complement diagnosis and to facilitate cascade screening, and emphasizes a thorough differential diagnosis. It provides recommendations for universal pediatric screening and systematic cascade screening in families to improve detection. Management strategies include intensified LDL-C treatment goals for both primary and secondary prevention of ASCVD. A stepwise approach to optimal therapy is outlined, beginning with lifestyle interventions and pharmacotherapy with maximally tolerated statins and ezetimibe. This update incorporates newer agents, including proprotein convertase subtilisin/kexin type 9 inhibitors and bempedoic acid. Additional therapies, such as lomitapide and evinacumab for homozygous FH and lipoprotein apheresis for heterozygous and homozygous FH, are discussed. Further topics include cardiovascular imaging for risk stratification, management in specific populations and circumstances, such as planning for and during pregnancy and in pediatrics, and recognition of health disparities. This guidance equips clinicians with evidence-based strategies to improve the identification and care of patients with FH, ultimately reducing the high morbidity and mortality associated with this condition.

Introduction

Familial hypercholesterolemia (FH) is a genetic disorder caused by decreased clearance of low-density lipoprotein (LDL) from the bloodstream due to inherited defects in the LDL receptor (LDLR) or associated proteins. These defects result in lifelong elevated LDL levels and a very high risk of early-onset atherosclerosis if left untreated.

FH is among the most common monogenic disorders worldwide. The pooled worldwide prevalence of the heterozygous form of FH is approximately 1 in 311 (0.32%), [1] while the homozygous form is considerably rarer, with an estimated global prevalence of around 1 in 300,000 individuals.[2]

In 2011, the National Lipid Association (NLA) published "*Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia*."[3] Since then, there has been remarkable progress in all of these areas. Here, we update this clinical guidance and provide clinicians with current insights and recommendations to effectively manage patients with FH and to reduce the associated high morbidity and mortality.

Definitions and diagnosis

Definitions

FH is broadly defined as *severe hypercholesterolemia (specifically elevated low-density lipoprotein cholesterol [LDL-C]), inherited in an autosomal semidominant pattern*.[3] In most families with FH, multiple generations will display severe hypercholesterolemia. Guidelines typically define this as LDL-C levels ≥190 mg/dL in adults and ≥160 mg/dL in children aged 5 years or older (or ≥130 mg/dL if there is a family history of early-onset atherosclerotic cardiovascular disease [ASCVD] or elevated LDL-C in 1 parent).

These LDL-C cutoffs should be considered rough guides since some carriers of FH with pathogenic/likely pathogenic (P/LP) variants can have LDL-C levels below these thresholds. Some individuals with polygenic hypercholesterolemia may have lifelong elevations in LDL-C similar to those with classic pathogenic variants in the *LDLR* gene, and some individuals with LDL-C above these levels do not have FH.[4] Notably, only about 5% or 6% of adults with isolated LDL-C levels > 190 mg/dL have FH.

The severity of the FH phenotype depends on the number of alleles affected, with individuals classified as either heterozygous, possessing one copy (monoallelic) of a pathogenic variant, or homozygous, having two (biallelic) pathogenic variants in *LDLR* and/or one of the other FH-related proteins (see below). Additionally, the severity of the FH phenotype depends on degree of dysfunction of LDLR activity caused by a specific pathogenic variant (e.g. null variants result in a more severe pheontype than missense variants). Heterozygous FH (HeFH) generally have pathogenic variants that reduce LDLR activity by > 75%. Homozygous FH (HoFH) is rare and more severe, often manifesting with extremely high LDL-C levels (typically > 400 mg/dL, up to 1200 mg/dL) and the potential for ASCVD in early childhood.

Diagnosis

All patients suspected of having FH should undergo a thorough review of medical and family history (age of onset

of hypercholesterolemia, secondary causes, and family and social history), physical examination (to identify premature corneal arcus, tendon xanthomas, and xanthelasma), and comprehensive laboratory evaluation (including lipid panels, lipoprotein(a) [Lp(a)], liver function tests, thyroid function tests, and urine protein). A clinical diagnosis of FH is made based on clinical characteristics, exclusion of secondary causes and phenocopies, severity of LDL-C elevation, and/or genetic testing. Genetic testing is not required to establish a diagnosis of FH, but such testing is appropriate to complement the clinical diagnosis and facilitate cascade screening (see Genetics section below).[5]

ICD-10 codes update

When a patient is formally diagnosed with FH, the appropriate International Classification of Diseases, Tenth Revision (ICD-10) code should be assigned (Table 1). This ensures that all members of the care team are aware of the diagnosis and will incorporate it into therapeutic planning. Further, such annotation can assist with registry research and population health efforts regarding FH, as well as the appropriate use of and access to specific therapies. It is important to ensure that these diagnosis codes are correctly applied by experienced clinicians only to patients with FH.

Diagnostic criteria

There are several potential strategies for establishing a diagnosis of FH. Some methods have been validated by comparison to genetic confirmation of FH, while others have been developed based on expert opinion or consensus. Although genetic testing is considered by some individuals to be the "gold standard" for diagnosis of FH, the sensitivity of genetic testing for diagnosis of FH may be as low as 60% among individuals who fulfill clinical criteria for a definite diagnosis of FH. Thus, some families with FH may not have an identifiable pathogenic variant known to cause FH. Although the diagnosis of FH is straightforward in many cases, there can be considerable nuance in the application and interpretation of diagnostic criteria in some patients.

Several clinical diagnostic criteria have been developed to assist in identifying individuals with heterozygous FH (HeFH).[6] The most widely used, accepted, and longstanding clinical diagnostic criteria include the U.S. Make Early Diagnosis to Prevent Early Death (MEDPED),[7] the Dutch Lipid Clinic Network (DLCN),[8] and the Simon Broome Registry criteria.[3,9] In addition, the NLA[3] and the American Heart Association (AHA)[10] have proposed alternative diagnostic frameworks, and other country-specific or regional guidelines have been developed.[11] Features of some of these diagnostic criteria for HeFH are summarized in Table 2.

While these tools support the FH diagnosis, strict adherence to a specific scoring system is not required. A clinician's diagnosis of FH, based on generally accepted standards of medical practice (incorporating personal and family history, physical findings, and lipid levels), is clinically appropriate and sufficient to substantiate the diagnosis for coverage of appropriate diagnostic evaluation (eg, genetic testing, advanced imaging), therapeutic procedures (such as lipoprotein apheresis), and the initiation and intensification of lipid-lowering therapies. In the United States, most providers with expertise in FH utilize a "clinical diagnosis" without the direct use of any scoring systems.[13]

Homozygous FH

A clinical diagnosis of HoFH is made independently of the commonly used diagnostic algorithms, such as DLCN, which were not designed for the diagnosis of HoFH. The presence of LDL-C > 400 mg/dL, the appearance of xanthomas in pediatric age (typically before age 10 years), and/or LDL-C levels compatible with HeFH in both parents, together with the absence of secondary causes, are sufficient to make a diagnosis of HoFH.

However, it is important to remember that HoFH may also be inherited as an autosomal recessive condition (see below). In this case, parents may have normal LDL-C levels. A clinical diagnosis of HoFH does not require genetic confirmation. Conversely, negative genetic testing, or the identification of only a heterozygous pathogenic variant, does not invalidate a clinical diagnosis of HoFH.

Physical examination

When present, certain physical signs support the diagnosis of FH and are incorporated into the DLCN score. However, the absence of characteristic physical examination signs does not exclude the diagnosis of FH. The likelihood and prominence of these signs correlate with the degree of LDL-C elevation and the duration of the individual's exposure to these elevated levels. More than half of patients with genetically confirmed FH do not have tendon xanthomas.[3] Furthermore, even when present, the findings can be subtle and easily missed without careful examination.[14]

Table 1. ICD-10 codes for FH, expanded in 2025 to provide the distinction between heterozygous and homozygous FH.

Code	Official description	Common use
E78.010	Homozygous familial hypercholesterolemia	HoFH
E78.011	Heterozygous familial hypercholesterolemia	HeFH
E78.019	Familial hypercholesterolemia, unspecified	FH (unspecified)

Note: The parent code E78.01 (familial hypercholesterolemia) is no longer the most specific code to use. Clinicians should use one of the specific codes listed above.

Abbreviation: ICD-10, International Classification of Diseases, Tenth Revision.

Table 2. Comparison of diagnostic criteria for the diagnosis of FH. Adapted from McGowan et al.[12]

Criteria[a]	MEDPED	DLCN	Simon Broome	NLA	AHA	Expert clinical diagnosis[b]
Family history of premature CAD		+	+	+	+	+
Family history of tendon xanthomas		+	+			+
Family history of hypercholesterolemia	+	+	+	+		+
Patient premature CAD		+		+		+
Patient premature PVD		+				+
Tendon xanthomas[c]		+	+	+		+
Corneal arcus (age < 45 y)		+		+		+
Elevated LDL-C	+	+	+	+	+	+
Genetic mutation		+	+	+	+	+

Abbreviations: AHA, American Heart Association; CAD, coronary artery disease; DLCN, Dutch Lipid Clinic Network; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; MEDPED, Make Early Diagnosis to Prevent Early Death; NLA, National Lipid Association; PVD, peripheral vascular disease.

[a]Features that may be considered by an expert clinician to inform a diagnosis of FH.

[b]These are the criteria that may be considered when establishing a diagnosis of FH using these diagnostic systems. Some or all of these criteria may be present in patients who are diagnosed with FH.

[c]Note that the Japan Atherosclerosis Society recommends assessment of Achilles tendon thickness with diagnostic thresholds of ≥8.0 mm in men and ≥7.5 mm in women by x-ray, or ≥6.0 mm in men and ≥5.5 mm in women by ultrasound.[11]

Tendon xanthomatosis is most commonly manifested as tendon thickening but may progress to include palpable or visible nodularity. Xanthomas, which represent the accumulation of cholesterol in macrophages, are nearly pathognomonic for FH.[15] Common locations include the Achilles tendons and the extensor tendons of the hands. Palpation may be necessary for detection, as they are often not visually prominent, particularly in individuals with HeFH. Radiological assessment of the Achilles tendon diameter ≥8.0 mm in men and ≥7.5 mm in women is highly correlated with a genetic diagnosis of FH and the prevalence of ASCVD, but it is often not detectable on physical examination.[16] In addition, given earlier and widespread initiation of statin medications, clinically apparent tendon xanthomas may be less evident on a population level than in the prestatin era because LDL-C lowering helps prevent xanthoma formation and may induce very slow regression.

Xanthelasmas are yellowish, often slightly raised cholesterol deposits that appear on or around the eyelids. While they can indicate high serum cholesterol levels, xanthelasmas are not specific to FH and can also occur in individuals with normal lipid profiles.[15]

Corneal arcus is a grayish-white or yellowish deposit of lipid material at the periphery of the cornea, separated from the sclera by a thin border of clear corneal tissue.[17] This lipid deposition typically begins superiorly and inferiorly and can progress to form a complete circumferential ring around the iris. The presence of corneal arcus in individuals younger than 45 years (sometimes referred to as arcus juvenilis) is particularly suggestive of underlying severe hyperlipidemia and should prompt a clinical workup for FH. In contrast, corneal arcus is a common finding in older adults (often referred to as arcus senilis) and is frequently associated with the aging process or with FH.[17,18] LDL-C x age is proportional to the development of corneal arcus.

Differential diagnosis

In evaluating individuals with elevated LDL-C, particularly those with levels ≥190 mg/dL, it is essential to exclude secondary causes of hyperlipidemia, which may be present in approximately 20% to 30%. The most important secondary causes are high-saturated fat + very-low-carbohydrate diets (eg, "keto," "carnivore"), nephrotic syndrome, hypothyroidism, obstructive liver disease, and various medications (eg, cyclosporin).[19] All patients with severe hypercholesterolemia should undergo evaluation for these secondary causes via detailed medical history, physical examination (eg, thyroid exam), and appropriate laboratory testing (eg, thyroid-stimulating hormone, creatinine, urine protein, and liver function tests). In addition, menopause occasionally can be associated with substantial increases in LDL-C, resulting in some women acquiring an FH-like lipid phenotype with LDL-C > 190 mg/dL despite lower LDL-C levels before menopause.

Phenocopies (phenotypic traits or diseases that resemble the trait expressed by a particular genotype but in an individual who is not a carrier of that genotype), albeit rare, should be considered in individuals with severe hypercholesterolemia (see Genetics section below). Of note, most phenocopies are inherited in an autosomal recessive manner, and family history may not reveal many affected individuals, aside from affected siblings. In addition, some features of FH, such as tendon xanthomas, may occur in other rare conditions in the absence of severe hypercholesterolemia (see Genetics section below). Notably, xanthomas—without high LDL-C levels—can be seen in some individuals with monoclonal gammopathy of undetermined significance (MGUS) who develop necrobiotic xanthogranuloma.

In some instances, missing information may limit the ability to formally diagnose FH using the diagnostic criteria. Some individuals, especially those who are adopted, may not be aware of their family history. Other individuals may already be taking lipid-lowering therapy (LLT), and untreated LDL-C levels may not be available. However, it is possible to estimate the untreated LDL-C level using an online calculator.[20] If the suspicion for FH remains high based on available data, such patients should be offered testing (eg, genetic testing, imaging) and provided treatment similar to FH.

Genetics

Genetic testing is indicated as a tool to complement a suspected or clinical diagnosis of FH and to facilitate cascade screening.

A positive FH genetic test result provides an unambiguous diagnosis and enhances cascade testing of at-risk relatives.[21] If pathogenic variants are identified, all first-degree relatives should be genetically tested irrespective of phenotype. In addition, reproductive partners should also be tested if pregnancy is anticipated.

In individuals with HoFH, genetic testing results may facilitate access to some medications (eg, evinacumab and lomitapide) but are not required by Food and Drug Administration (FDA) approval criteria and are generally not required for insurance coverage.

While testing should be offered, clinical implementation may vary based on factors such as cost, test availability, patient preferences, and access to genetic counseling (see below).[5,22–24] Genetic testing is not required for diagnosis or clinical management of FH.[21] Individuals with severe hypercholesterolemia or clinically suspected FH are at very high risk of ASCVD (between 6- and 22-fold), irrespective of the precise genetic etiology.

Individuals with severe hypercholesterolemia and a confirmed P/LP variant carry nearly twice the ASCVD risk of those with severe hypercholesterolemia but no P/LP variants. Nonetheless, ASCVD risk in the variant-negative group remains substantially elevated and requires assertive treatment. Management should thus be based on the severity of LDL-C elevation, not on genotype.

Causative genes and terminology

The terminology for the genetic basis of FH has evolved over time and can be a source of confusion, but modernized terminology has been developed (Table 3). FH is a Mendelian disorder inherited in an autosomal semidominant (note: the term "codominant" is no longer recommended for FH) pattern with a gene dosage effect, meaning that individuals with one pathogenic variant (HeFH) typically have severely elevated LDL-C and an increased chance of developing clinical manifestations (eg, tendon xanthomas, ASCVD).[25,26] Individuals with pathogenic variants on two alleles (HoFH) typically exhibit LDL-C levels that are at least twice as elevated as those seen in HeFH, accompanied by more severe clinical manifestations from a younger age, including accelerated atherosclerosis, often within the first 2 decades of life.[25,26]

The main genes underlying FH are *LDLR* (85%-90% of cases), encoding LDLR; *APOB* (5%-15% of cases), encoding apolipoprotein (apo) B; and proprotein convertase subtilisin/kexin type 9 (*PCSK9*) (1% to 3% of cases), encoding PCSK9[26](Table 4).

A fourth gene, *LDLRAP1*, encoding the LDLR adapter protein 1 (LDLRAP1) that guides internalization of the LDLR, is a rare cause of HoFH and follows an autosomal recessive pattern rather than autosomal semidominant (Table 4). Therefore, "biallelic recessive hypercholesterolemia" should be used to identify the recessive form of HoFH caused by biallelic variants in *LDLRAP1*. Note that monoallelic (carrier/heterozygous) P/LP variants in *LDLRAP1* do not cause a significant lipid phenotype, including HeFH.[25]

A genetic diagnosis of HeFH is confirmed by the presence of a single P/LP variant in a single alelle of *LDLR*, *APOB*, or *PCSK9*, while HoFH is confirmed if P/LP variants affect two alleles (biallelic) of *LDLR*, *APOB*, *PCSK9,* or *LDLRAP1*.[25] Previous terminology for HoFH, such as

Table 3. Comparison of old and updated HoFH terminology.[25]

Old terminology	New terminology	Examples
True homozygote	Biallelic semidominant hypercholesterolemia, monogenic (same gene, same variant)	Same *LDLR* mutation from both parents
Compound heterozygote	Biallelic semidominant hypercholesterolemia, monogenic (same gene, different variants)	Different *LDLR* mutation from each parent
Double heterozygote	Biallelic semidominant hypercholesterolemia, digenic (2 different genes, 2 variants)	*LDLR* mutation and *APOB* mutation
Autosomal recessive hypercholesterolemia	Biallelic recessive hypercholesterolemia, single gene	*LDLRAP1* mutation from each parent

Abbreviations: *APOB*, apolipoprotein B gene; HoFH, homozygous familial hypercholesterolemia; *LDLR*, low-density lipoprotein receptor gene; *LDLRAP1*, low-density lipoprotein receptor adaptor protein 1 gene.

Table 4. Genetic causes of familial hypercholesterolemia and conditions that share features of familial hypercholesterolemia.

Gene	Inheritance pattern	Proportion of cases	Comments
Classical familial hypercholesterolemia (HeFH and HoFH)[25,26]			
LDLR	Autosomal semidominant	~85%-90%	Most common cause: pathogenic variants reduce LDLR function (null or defective alleles). Clinical severity varies by mutation type.
APOB	Autosomal semidominant	~5%-10%	Pathogenic variants impair the binding of LDL particles to LDLR. Typically, milder phenotype than LDLR mutations.
PCSK9	Autosomal semidominant	1%-3%	Gain-of-function mutations increase LDLR degradation. Less common and milder phenotype than *LDLR* mutations.
LDLRAP1 (HoFH only)	Autosomal recessive	Extremely rare (< 1% of HoFH)	Previously referred to as autosomal recessive hypercholesterolemia (ARH). LDLR is intact, but endocytosis is defective.
Other genetic causes that sometimes mimic Familial Hypercholesterolemia (phenocopies)			
APOE p.Leu167del variant[32,33]	Autosomal dominant	Isolated cases/families	Very rare cause; sometimes mimics FH phenotype.
ABCG5 and *ABCG8*[34–36] (sitosterolemia/phytosterolemia)	Autosomal recessive	Very rare	Increased plant sterol absorption; some patients are misdiagnosed as FH due to elevated LDL-C and xanthomas. Distinguishing feature: elevated plasma sitosterol levels (specialized testing).
LIPA (lysosomal acid lipase deficiency, LALD)[37]	Autosomal recessive	Very rare	Can cause high LDL-C and low HDL-C. Affected individuals have early onset hepatic steatosis and hepatosplenomegaly (due to accumulation of cholesterol esters within lysosomes); Tendon xanthomas typically absent.
CYP27A1 (cerebrotendinous xanthomatosis, CTX)[38–40]	Autosomal recessive	Very rare	LDL-C is usually normal; cholestanol is elevated. Presents with large tendon xanthomas, neurologic symptoms, and cataracts.
ALB (congenital analbuminemia, CAA)[41]	Autosomal recessive	Extremely rare	Profoundly low serum albumin levels with normal hepatic and renal function. LDL-C increased due to a compensatory increase in plasma proteins and altered lipoprotein metabolism.
Non-Mendelian hypercholesterolemia			
Polygenic hypercholesterolemia[42]	Complex/polygenic	30%-40% of clinically diagnosed FH	Due to the accumulation of common LDL-C–raising alleles; mimics HeFH clinically; there is no standardized clinical test for polygenic hypercholesterolemia at present.

Abbreviations: *ABCG5*, ATP-binding cassette subfamily G member 5 gene; *ABCG8*, ATP-binding cassette subfamily G member 8 gene; *APOB*, apolipoprotein B gene; *APOE*, apolipoprotein E gene; ARH, autosomal recessive hypercholesterolemia; FH, familial hypercholesterolemia; HeFH, heterozygous familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; HoFH, homozygous familial hypercholesterolemia; LDL, low-density lipoprotein; LDLR, low-density lipoprotein receptor; LDL-C, low-density lipoprotein cholesterol; *LDLRAP1*, low-density-lipoprotein receptor adaptor protein 1 gene; *PCSK9*, proprotein convertase subtilisin/kexin type 9 gene.

"true homozygote," "compound heterozygote," and "double heterozygote," has been superseded by more accurate genetic terminology, ie, "biallelic semidominant hypercholesterolemia, monogenic (same gene, same variant)," "biallelic semidominant hypercholesterolemia, monogenic (same gene, different variants)," and "biallelic semidominant hypercholesterolemia, digenic (2 different genes, different variants)."[25]

Genotype and phenotype is generally correlated in FH, but with substantial interindividual variability. *LDLR* variants are categorized as "null" (< 2% activity) or "receptor defective" (2%-70% activity). Individuals with *LDLR* null variants typically show the highest LDL-C levels and may be less responsive to treatment.[25,26] Patients with FH due to *APOB* pathogenic variants have a slightly milder LDL-C phenotype than those with *LDLR* variants.[25] When the

Table 5. Genetic counseling recommendations: when, who, why, and what to discuss.

When to provide genetic counseling	Who should receive genetic counseling and why	What to discuss during genetic counseling
Before genetic testing[5,21,52]	Patients with FH seeking diagnostic testing; at-risk family members seeking predictive cascade testing for a familial FH-causing variant	Informed consent: Discuss the implications of genetic testing and obtain informed consent. Provide education about the test to be undertaken, including the difference between lipid and genetic testing, outlining the benefits and limitations of both. Discuss the probability and meaning of possible results, protections, and limitations for patient privacy and confidentiality. Provide anticipatory guidance about potential psychosocial issues (anxiety, misunderstanding, family issues, guilt).[5,21,53] For individuals pursuing cascade testing, informed consent should include education about the probability of carrying the familial disease-causing variant, management based on possible results, and limitations. Focus on anticipatory guidance about potential psychosocial issues while waiting for or after receiving results. All individuals pursuing genetic testing should be informed about the cost and timing of results, as well as other logistics related to the genetic testing workflow.
After genetic testing[54,55]	Anyone who has undergone genetic testing for FH	Discuss results and management implications. Include a discussion of familial risk and cascade testing, if indicated.
Before pregnancy	Any person with FH who is considering carrying a pregnancy	Discuss the probability of having a child with FH and options for reproductive decision-making. Discuss medications, emphasizing the importance of appropriate therapy in collaboration with the prescribing clinician. Consider referrals for diet and lifestyle modifications, as well as apheresis in severe cases.
During pregnancy[25]	Any person with FH carrying a pregnancy	Discuss topics similar to pre-conception counseling. Referral to prenatal genetic counseling (usually in maternal-fetal medicine settings) may be necessary, particularly if there is a risk of HoFH in the fetus. In collaboration with a high-risk obstetrician, cardiology surveillance is indicated due to increased hemodynamic demands and the natural LDL-C rise during the second and third trimesters.[53]
For most patients and family members pursuing genetic testing		Inform about the cost and timing of results, as well as other logistics related to the genetic testing workflow.

Abbreviations: FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol.

genotype and phenotype are discordant, expert position statements advocate prioritizing the LDL-C phenotype over genetic findings.[27]

Several monogenic phenocopies of FH exist (Table 4) and are caused by genes not involved in the LDLR pathway.[25,26,28–31] These include: (1) heterozygosity for *APOE* p.Leu167del[32,33] (moderately elevated LDL-C), (2) sitosterolemia (phytosterolemia),[34–36] (3) lysosomal acid lipase deficiency,[37] (4) cerebrotendinous xanthomatosis,[38–40] and (5) congenital analbuminemia.[41] Some of these conditions cause hypercholesterolemia without physical features of FH, such as xanthomas, whereas others cause xanthomas without hypercholesterolemia. There are also clinical differences in most of these conditions that distinguish them from FH. Note that, other than the *APOE* variant, these conditions are inherited in an autosomal recessive manner. As a result, family history is often devoid of hypercholesterolemia, except in potentially affected siblings from the same parents.

Among individuals clinically suspected of having FH (see Definitions and diagnosis section above), 30% to 60% will have a positive genetic test identifying a P/LP variant

in *LDLR*, *APOB*, *PCSK9*, or *LDLRAP1*.[42,43] Conversely, 30% to 40% of suspected FH cases exhibit a high polygenic (non-Mendelian) risk score for LDL-C.[42] Polygenic hypercholesterolemia confers a risk of ASCVD comparable to monogenic FH, warranting similarly aggressive treatment, but it is generally not a cause of dominantly inherited hypercholesterolemia.[44]

Importantly, a negative genetic test for FH should not preclude appropriate treatment for FH or cascade screening for hypercholesterolemia in family members. It should be noted that some payers may attempt to deny coverage for treatment if genotyping for FH is negative, but negative genetic tests should not be used to deny clinically indicated testing and treatment.

Availability and cost of genetic testing

An ideal genetic testing panel for FH includes the 4 primary FH-associated genes (*LDLR, APOB, PCSK9* and *LDLRAP1*), as well as *APOE* and genes associated with phenocopies (*LIPA, ABCG5, ABCG8, CYP27A1,* and *ALB*). In addition, panels should include methods to detect copy number variants - such as large deletions or duplications - especially in *LDLR,* since such variants were frequently missed by older sequencing techniques.

Some "FH" panels only test a limited set of variants within the *LDLR* gene. We do not recommend these panels since over 800 P/LP variants in *LDLR* have been identified to date, and new variants continue to be identified. Recently, a comprehensive sequence–function map was published that characterizes the functional impact of nearly all possible missense variants in *LDLR*, providing a critical resource to help resolve variants of uncertain significance (VUSs) and improve risk inference[45]; this work identified roughly 2000 coding variants that are potentially pathogenic. Thus, comprehensive sequencing is essential to ensure accurate genetic diagnosis and avoid missed pathogenic findings, including large deletions and sequence duplications.

Notably, a VUS often causes confusion. Rarely, a VUS may represent a novel pathogenic variant, but the majority of VUSs are found to be benign when reclassified. ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) serves as the primary repository for reclassification of VUSs, utilizing criteria beyond simple algorithmic prediction. Since most VUSs are found to be nonpathogenic, patients should be counseled that a VUS finding is not diagnostic, even when identified in the gene of interest (like *LDLR).*

The cost of testing can be a primary barrier for some patients. In the United States, the cost of genetic testing for FH varies depending on the patient's payer coverage and the pricing policies of the testing company. While the list price for comprehensive panels can reach several thousand dollars, Medicaid—depending on the state in the United States—may offer testing to qualified patients without additional charge to the patient. For others, out-of-pocket costs range from $100 to $500.[46] When not covered by payers, the cost of genetic testing may exceed $2000; hence, payer coverage should be verified by genetic testing labs before testing.

Access to genetic testing is often limited by the availability of, and access to, clinicians with the necessary expertise and comfort in determining the indications for testing, as well as in providing pretest and posttest counseling.

Genetic counseling

For FH, the Consent and Disclosure Recommendations Workgroup, a group of genetics clinicians and bioethicists, recommends targeted discussions about genetic testing supported by educational resources and a brief assessment of the need for more involved communication.[47]

These communications could be completed by any clinician, provided they collaborate or consult with a genetics expert when needed.[48] Clinicians should understand test ordering logistics and the key elements of informed consent.[47,48]

Pretest counseling should include education about the test and a brief assessment of whether more detailed consultation is required (Table 5).[47,48] Clinicians should explain the purpose of genetic testing: to complement a clinical or suspected diagnosis of FH and to enable cascade screening. The discussion should cover what the test analyzes, potentical genetic discrimination (see below), and possible outcomes. Possible outcomes include "positive" (a P/LP variant is found), "negative" (no P/LP variant found; does not rule out FH), or "VUS." Clinicians should also discuss limitations, noting that some families with FH may not have identifiable variants, and emphasize that treatment decisions are based on LDL-C levels and clinical risk, not just on genotype.

Posttest counseling should focus on explaining results in plain language, addressing patient questions, and determining whether referral for comprehensive genetic counseling is needed.[47,48] Patients with genetic testing results that are complex or challenging to interpret (eg, a novel VUS that is suspicious for pathogenicity) should be referred to a genetic counselor or a clinician with genetics and lipidology expertise for further evaluation and guidance.[21,25,49,50]

Individuals with HoFH require specific counseling considerations, including complex genotype–phenotype correlations, the need to start intensive LDL-C lowering therapy at the time of diagnosis, and pregnancy health and reproductive options. They may also benefit from traditional genetic counseling.[25,51]

As needed, genetic counselors can be found at https://findageneticcounselor.nsgc.org and https://abgc.learningbuilder.com/Search/Public/MemberRole/Verification.

Genetic discrimination

Genetic discrimination is the unfair treatment of individuals based on their genetic information, particularly those who are asymptomatic.[56] Federal laws, such as the

Americans with Disabilities Act and the Affordable Care Act (ACA), prohibit genetic discrimination against individuals who are symptomatic (ie, someone with severe hypercholesterolemia). The potential for discrimination is a larger issue for individuals who carry FH-causing variants but are "asymptomatic" (ie, individuals who carry FH-causing genetic variants but do not have severely elevated cholesterol).

The Genetic Information Nondiscrimination Act (GINA), enacted in 2008, prohibits discrimination based on genetic information in health insurance and employment.[57] However, GINA does not extend to life, disability, or long-term care insurance. Another key limitation of GINA is its narrow definition of genetic information, which includes only an individual's genetic test results, the genetic test results of family members of the individual, and the manifestation of a disease or disorder in family members of the individual.[58] Importantly, GINA does not protect individuals who have already manifested a disease; thus, it does not prohibit discrimination against already-affected individuals. In contrast, the ACA, enacted in 2010, prohibits discrimination in health insurance due to preexisting health conditions, whether genetic or nongenetic. As a result, the ACA currently provides broader and more efficient protection against genetic discrimination in health insurance than GINA.

Because federal legislation prohibits genetic discrimination in health insurance and employment, life insurance is the largest area without legislative protection. In 2020, Florida became the first and still the only state to enact a law prohibiting genetic discrimination in life insurance.[59] Unlike Australia, Canada, France, Germany, South Korea, the United Kingdom, and other countries, the United States does not have national legislation prohibiting genetic discrimination in life insurance. Notably, in countries that have enacted such laws, there is no evidence of significant negative consequences, including unavailability of insurance, substantial price increases, or adverse impacts on the financial stability of life insurance providers.[60]

FH screening

Adult screening

Several organizations, including the NLA, recommend opportunistic testing for FH in all adults. Valuable strategies include electronic health record tools that involve algorithmic case-finding, automated laboratory report alerts for high LDL-C, and machine learning models.[61–67] Broader, population-based efforts have included large-scale blood donor programs to screen for FH by measuring total cholesterol in donors and applying age-specific levels (eg, MEDPED criteria).[68]

While these tools can effectively flag patients who potentially have FH, a formal diagnosis must be confirmed using validated clinical criteria or genetic testing, as algorithm accuracy varies.

Pediatric screening

We and others, such as the Family Heart Foundation and the American Academy of Pediatrics, recommend universal lipid screening for all children aged 9 to 11 years, consistent with national guidelines.[69] Screening should occur earlier (from age 2 years) if there is a family history of hyperlipidemia or early-onset ASCVD, and even earlier when both parents have HeFH.

Early identification of FH in childhood is critical for timely intervention, yet real-world testing rates remain unacceptably low.[70] Barriers to pediatric testing exist at the clinician, patient, and system levels. These include logistical challenges in busy practices, provider discomfort with prescribing LLTs, and low patient adherence.[71–74] A few organizations continue to discourage screening for lipid disorders in children, which adds confusion about the importance of screening. Simplifying testing (eg, using nonfasting, point-of-care tests) and improving provider education and referral pathways are critical steps to overcoming these hurdles.

Cascade screening

We recommend cascade screening for all first- and second-degree relatives of patients with a confirmed FH diagnosis.[22,23,75–79] This process should use lipid measurements and, if a proband has an identifiable pathogenic variant, genetic testing for that specific variant. Cascade screening is the most cost-effective strategy for identifying new FH cases, allowing for timely intervention to reduce cardiovascular risk.

Despite its value, the uptake of cascade screening in the United States is low,[80–83] largely because relying on probands to contact relatives is often ineffective.[5,10] We suggest a proactive approach where healthcare professionals/systems, with patient consent, directly contact family members. This method, ideally supported with adequate resources, significantly improves screening uptake and should be the standard of care.[83–90]

ASCVD risk stratification

ASCVD risk varies among individuals with FH due to multiple factors, including the following:

- Underlying genotype.
- Severity and duration of exposure to cholesterol and Lp(a).
- Susceptibility of the artery wall to plaque formation.
- Concomitant risk factors (eg, diabetes, hypertension, smoking).
- Age at initiation and intensity of LDL-C lowering medications.
- Other influences, such as epigenetic factors.

ASCVD risk calculators

Standard cardiovascular risk calculators, such as the Pooled Cohort Equation and Predicting Risk of Cardiovascular Disease

EVENTs (PREVENT) equations, should not be used for patients with FH, as stated in multiple guidelines.[79,91,92] These tools are designed for the detection of risk in the general population and will dramatically underestimate risk in FH, as they do not account for the lifelong, severe cumulative LDL-C exposure that defines the disease.

While FH-specific calculators (eg, Spanish Familial Hypercholesterolemia Cohort Study Risk Equation [SAFEHEART-RE], FH-Risk-Score) have been developed to address this gap, they have significant limitations.[93–100] They are not widely validated across diverse populations, may not be generalizable, and often omit key risk-enhancing factors.

We emphasize that risk stratification in FH must include a comprehensive clinical assessment and that clinical judgment is paramount. The presence of ASCVD risk factors/enhancers and assessment of clinical symptoms should be the primary guide for therapeutic intensity. These factors include—but are not limited to—a strong family history of early-onset ASCVD and an elevated Lp(a) level, which is a powerful independent predictor of ASCVD risk in the FH population. We recommend assessing these factors, as well as imaging and other diagnostic evaluations if indicated (eg, cardiac stress testing, echocardiography, etc), to fully characterize risk and guide shared decision-making regarding choices of therapy and treatment intensity.

Use of cardiac imaging in patients with FH

Coronary artery calcium scoring

Given that patients with FH have high levels of exposure to atherogenic lipoproteins since birth and have a high lifetime risk of atherosclerosis, the absence of plaque on an imaging study at any 1 time point should not be used to stop or delay LLT. Moreover, since most plaque is not calcified, the absence of calcified plaque should not be interpreted as no plaque, particularly in patients with FH.

Coronary artery calcium scoring (CACS) is a widely used tool to further stratify risk in patients with FH, who are already in a high ASCVD risk group, and to obtain prognostic information. When present, CAC is predictive of cardiovascular events in patients with HeFH (Fig 1), much as in the general population. In several studies of individuals with FH, with mean ages (years) in the 40s and 50s, 54% to 65% had prevalent CAC.[101–104] Higher CAC scores correlated with significantly increased risk, independent of traditional risk factors.[103,104] The finding of a screening CAC value of >0 may be used as an indication to intensify LLT, especially in younger patients.

The absence of CAC in HeFH implies a lower short-term risk for about 4 years, as opposed to the general population, where the period is about 5 to 8 years.[101,105] Critically a CAC score of 0 does not guarantee the absence of atherosclerosis or short-term ASCVD risk for individuals with FH. Myocardial infarction can still occur in FH patients with a CAC score of 0. As such, LDL-C goals for primary prevention should not be altered for individausl with FH and a CAC of 0.

Atherosclerosis screening in HeFH is usually done after age 20 to 30 years and depends on various clinical features (Table 6) that determine whether plaque is likely to be present by that age and is likely to be detected by the imaging test being used, whether cardiac computed tomography angiography (CCTA) or CACS. In general, CCTA will detect noncalcified plaque about a decade before CAC is detectable in younger individuals.[104]

Similar to other recommendations,[106] we recommend that CACS should not be used to monitor the effectiveness of cholesterol-lowering therapy (Class I—strong; level of evidence B—moderate). This is because once plaque becomes calcified, intensive LLT (such as with statins) and aging both lead to an increase in the absolute CAC score over time, rather than a decrease. Moreover, healing and resolution of noncalcified plaque in response to LLT is associated with an increase in calcified plaque that is proportional to a reduction in ASCVD events. Dense calcification occurring within the same plaque is thought to be protective, whereas plaques that are the culprit lesions in acute coronary syndromes (ACS) are usually noncalcified or have both mixed calcific and noncalcified (lipid-rich) elements.[107]

Cardiac computed tomography angiography

CCTA can detect noncalcified plaque prevalent in younger individuals and can also allow assessment of the coronary fractional flow reserve, which is a measure of net perfusion in a specific artery.[108] Factors that may warrant screening in an asymptomatic patient with HeFH or workup in a symptomatic individual are listed in Table 6.[109]

Studies have shown a high prevalence of coronary artery plaque in patients with FH, sometimes identifiable as early as the 20s and 30s, with plaque burden being predictive of major adverse cardiovascular events (MACE).[110–113] Notably, even in statin-treated patients with FH and controlled LDL-C, a significant proportion may still exhibit high-risk plaque on CCTA.[109,113]

Data from observational studies suggest that CCTA screening can lead to intensification of LLT and other preventive measures, potentially reducing risk.[114] Furthermore, intensive LLT, particularly when initiated early, has shown promise in achieving plaque regression in a small study of patients with HoFH.[115]

Children and adults with HoFH frequently develop aortic valve stenosis and severe coronary ostial stenosis, and rarely supravalvular stenosis, which can remain asymptomatic until ACS or sudden death occurs. Because the mean age of first cardiac event is 12 years in untreated children with HoFH, consideration should be given for performing a baseline assessment of the atherosclerotic burden with CCTA, as well as echocardiography in children and adults at the time of diagnosis of HoFH.

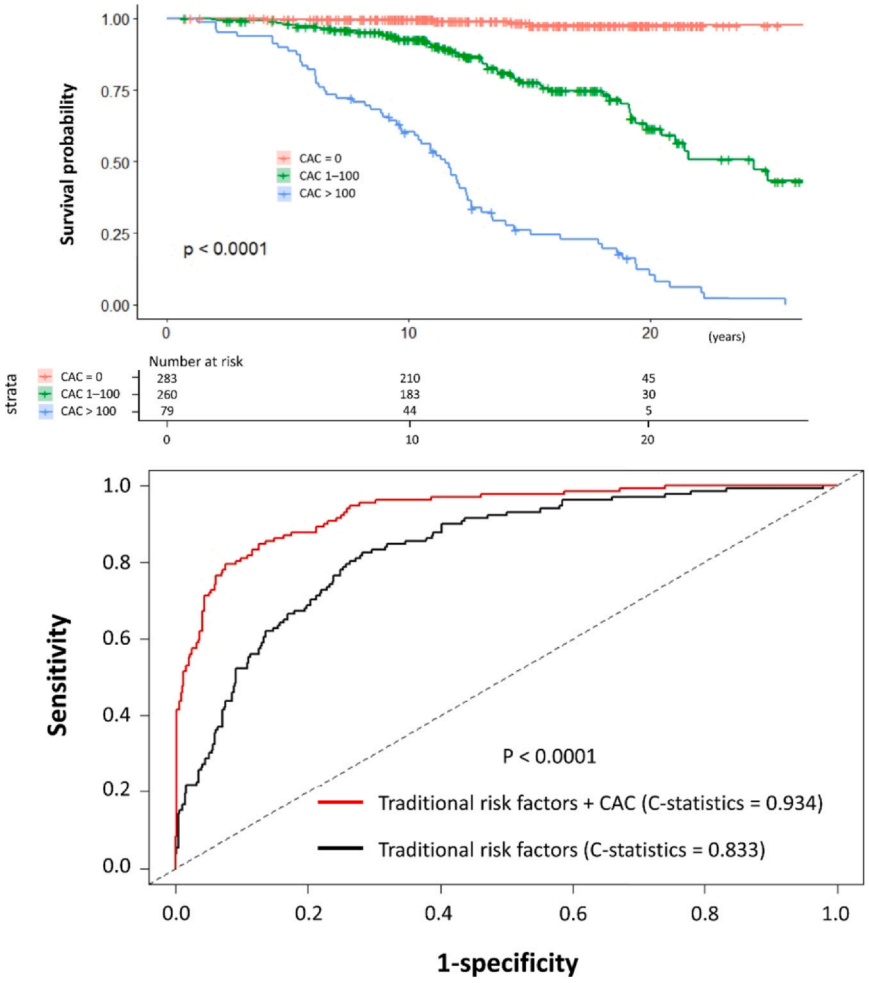

Figure 1. Coronary artery calcium scoring and cardiovascular outcomes in individuals weith FH. Top panel: Kaplan–Meier curve showing increased risk of the primary endpoint (cardiovascular death or unstable angina, myocardial infarction, or revascularization) with increasing tertiles of CACS in more than 600 primary-prevention patients with FH. Note: the high survival observed in the CAC = 0 group (mean age 47+/- 12 years) occurred in the context of ongoing lipid-lowering therapy (median achieved LDL-C 108 mg/dL). These data characterize the prognostic value of CACS for short-term risk but do not support the deferral of therapy in FH, as lifelong cumulative LDL-C exposure remains the primary driver of risk. Lower panel: Addition of CACS to traditional ASCVD risk factors improved the discrimination (C-statistic) for the primary endpoint. Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CACS, coronary artery calcium score; FH, familial hypercholesterolemia.
Reproduced with permission from Tada et al.[103]

Table 6. Factors that favor the use of CCTA to screen for ASCVD in FH.

Severe genotype (null mutation)
Higher cholesterol years of exposure (LDL-C x age)
Male gender
Family history of early-onset ASCVD or sudden cardiac death
Concomitant risk factors that elevate overall risk—elevated Lp (a), smoking, diabetes, etc.
Concern for ischemic symptoms

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CCTA, cardiac computed tomography angiography; FH, familial hypercholesterolemia; Lp(a), lipoprotein(a); LDL-C, low-density-lipoprotein cholesterol.

Treatment

Goals and targets

LDL-C treatment goals for the prevention of cardiovascular disease have substantially intensified over the last 30 years, in large part thanks to the documented benefit of sequentially lower LDL-C levels for the prevention of ASCVD events and the ongoing development of new LLTs leading to the ability to reach lower LDL-C goals. The goals listed below are based on clinical trial evidence documenting ASCVD risk in proportion to achieved LDL-C levels, evidence from human Mendelian randomization

Table 7. Recommended treatment goals.

Patient population	Recommended LDL-C goal (mg/dL)	Non–HDL-C goal (mg/dL)	Apo B goal (mg/dL)	Additional requirement
Secondary prevention (adults with FH + ASCVD or high plaque burden)	< 55	< 85	< 55	≥50% reduction from baseline
Recurrent event (2nd event within 2 y)	< 40			≥50% reduction from baseline
Extreme risk (South Asian ethnicity)	< 30			≥50% reduction from baseline
Primary prevention (adults with FH)	< 70	< 100	< 70	≥50% reduction from baseline
Pediatric FH (heterozygous)	< 100			≥50% reduction from baseline
Pediatric FH (homozygous)	< 100 (primary prevention) < 70 (with ASCVD)			≥50% reduction from baseline

Abbreviations: Apo B, apolipoprotein B, ASCVD, atherosclerotic cardiovascular disease; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; Non–HDL-C, non–high-density lipoprotein cholesterol.

Note: For patients with statin intolerance, the LDL-C goals remain the same. "Primary Prevention" in FH may include patients with subclinical atherosclerosis identified on imaging who have not yet had a clinical event; treatment goals should be aggressive in these individuals. Apo B goals derived from equivalent risk levels in major guidelines (eg, 2019 European Society of Cardiology/European Atherosclerosis Society).

genetic studies, and previous guideline recommendations (Supplementary Table S1).

All patients with FH should achieve at least a 50% reduction from baseline LDL-C levels as a minimum initial threshold; however, the ultimate objective is to reach the specific LDL-C goals outlined below (Table 7).

Note that the lowest median LDL-C levels achieved in clinical trials of LLT with PCSK9 inhibitors were 30 mg/dL. Although these data were not specific to individuals with FH, these very low LDL-C levels were achieved in a secondary prevention cohort in the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial (evolocumab)[116] with no clear safety signal in 2 to 5 years of follow-up, even for LDL-C < 10 mg/dL. For individuals with FH, achieving LDL-C < 30 mg/dL is less common due to higher baseline LDL-C levels, but the evidence from general high-risk populations, such as in Evaluation of Evolocumab in Patients Without Prior Myocardial Infarction or Stroke (VESALIUS-CV),[117] supports aggressive and sustained LDL-C lowering. Moreover, the risk of ASCVD events is proportional to the achieved LDL-C concentration down to 20 mg/dL or lower, suggesting that achieving LDL-C levels far below current goals may be beneficial in the highest-risk individuals.

Optimal duration and maintenance

Lifelong treatment of FH is recommended. Evidence strongly supports that LLTs should be initiated as early as possible—ideally in childhood—and maintained at target levels continuously and lifelong, as both the degree and duration of LDL-C exposure (cumulative LDL-C burden, estimated by the integral of LDL-C x age) are critical determinants of ASCVD risk.[118,119] Data from the Netherlands show that early treatment of children with FH led to complete or nearly complete protection from atherosclerosis, in marked contrast to the high prevalence of ASCVD in their parents who did not have the benefit of early initiation of LLT.[118]

Secondary prevention, adults with FH

LDL-C should be reduced to < 55 mg/dL, corresponding to a non–high-density lipoprotein cholesterol (non–HDL-C) goal of < 85 mg/dL and an apo B goal of < 55 mg/dL. Although secondary prevention often focuses on individuals who are classified based on having a history of myocardial infarction, stroke, or revascularization, it is reasonable to apply the same treatment goals to patients with FH who have an elevated plaque burden (eg, abnormal CACS or coronary CTA, or percutaneous coronary angiography) before the occurrence of any ASCVD event.

A lower LDL-C target of < 40 mg/dL is reasonable for those with FH who experience a second vascular event within 2 years despite maximal therapy.[120]

An even lower goal of < 30 mg/dL is reasonable for South Asian individuals with extreme-risk FH, given the high background ASCVD risk prevalent in this population.[121]

Among all patients with ASCVD, it is well documented that the risk of ASCVD events is proportional to the achieved LDL-C concentration down to < 20 mg/dL without any additional safety signal.[122,123]

Primary prevention, adults with FH

We recommend an LDL-C goal of < 70 mg/dL, corresponding to non–HDL-C goals of < 100 mg/dL and apo B

< 70 mg/dL. The LDL-C goal of < 70 mg/dL in FH in lieu of the previous < 100 mg/dL goal in primary prevention is a consequence of the high risk of ASCVD in patients with FH and recognition that patients with FH without ASCVD who achieve a mean LDL-C concentration of 100 mg/dL still have an unacceptably high risk of incident ASCVD events.[79,124]

Homozygous FH, adults

Among adults with HoFH, it can be very challenging to achieve these LDL-C goals due to severely elevated baseline LDL-C concentrations and hyporesponsiveness to many LLTs Clinicians need to take advantage of every available LLT, including lomitapide and evinacumab, which are FDA-approved only for the treatment of patients with HoFH, and lipoprotein apheresis (see Homozygous FH section).

HeFH, children and adolescents

We recommend an LDL-C goal of < 100 mg/dL in children and adolescents with FH. Long-term follow-up studies demonstrate that achieving and maintaining LDL-C below 100 mg/dL in children with FH is associated with normalization of vascular risk markers and near-elimination of early-onset ASCVD in adulthood, underscoring the importance of early and persistent LDL-C lowering.[118] Treatment can begin at age 8 to 10 years or possibly earlier if there is a family history of very early onset of ASCVD events.

Homozygous FH, children and adolescents

Among children and adolescents with HoFH, the recommended LDL-C goal is < 100 mg/dL in primary prevention.[25,118,125] For those with a history of ASCVD events, the goal is < 70 mg/dL or the lowest achievable level. About 50% of patients with HoFH with an LDL-C concentration of 70 mg/dL still experience plaque progression, suggesting LDL-C of 70 mg/dL may be insuffcient in many patients with HoFH and ASCVD.

FH and statin intolerance

For individuals with FH and statin intolerance, the LDL-C goals do not change. In these situations, *shared decision-making* becomes critical and is an essential framework for navigating this challenge.

Patients with FH with apparently low ASCVD risk

Within the primary prevention FH population, there is a spectrum of ASCVD risk. After stratifying ASCVD risk with tools such as a detailed ASCVD family history, Lp(a) levels, CAC/CCTA imaging, apo B levels, and perhaps a polygenic risk score for CAD, a patient with FH may appear to be at low risk (eg, young, CAC score=0, no other risk factors). However, the long-term LDL-C goal remains the same (< 70 mg/dL) because their lifetime ASCVD risk remains high.

Lifestyle and dietary recommendations

Several clinical guidelines outline a healthy dietary pattern for the reduction of atherogenic lipoprotein levels, emphasizing the importance of lifestyle modification as the foundation of ASCVD prevention.[23,79,126,127,130–134] Table 8 includes nutrition and lifestyle recommendations outlined in the recent NLA clinical perspectives for youth and adults with dyslipidemia, including those with FH.[126,127]

For individuals with FH, lifestyle modification alone is rarely sufficient to achieve LDL-C targets.[3] A few population-based and case-control/cohort studies confirm that a heart-healthy diet and favorable lifestyle can reduce ASCVD risk in individuals with FH and allow for modest reductions in the intensity of LLT. Furthermore, implementation of a cardioprotective dietary pattern addresses other ASCVD risk factors, such as hypertension and type 2 diabetes mellitus.[133]

Nutrition recommendations are similar for those with HoFH and HeFH. Nutrition interventions should be individualized, and referral to a registered dietitian nutritionist for medical nutrition therapy is recommended.[126,127,130]

Individuals with HoFH who are treated with lomitapide require specialized dietary recommendations that include restriction of dietary fat intake and supplementation with essential fatty acids.

Dietary adjuncts

Clinicians should routinely inquire about the use of dietary adjuncts, including herbal and over-the-counter supplements. Among available supplements, only viscous soluble fiber and plant sterols/stanols have clear and consistent evidence for modestly lowering LDL-C. In the unusual circumstance that LDL-C markedly increases with the use of plant sterol/stanol supplementation, sitosterolemia should be suspected.[126]

Red yeast rice, although commonly marketed for LDL-C lowering, is not recommended due to considerable variability in its LDL-C–lowering response, lack of regulatory oversight, inconsistent dosing, and unknown purity or level of contamination.[127,135] It is also much more expensive than generic statins obtained through a pharmacy.

Similarly, coenzyme Q10, a product marketed to assist with lowering statin-associated muscle symptoms, is not recommended because it lacks long-term safety and efficacy data, particularly in youth.[79,126,136,137]

Medications

Table 9 and Table 10 provide details on LLT medications available for the treatment of FH.

Statins

Patients with FH should be treated with a high-intensity statin consisting of atorvastatin 40 to 80 mg daily or

Table 8. Summary of nutrition and lifestyle interventions for cardiovascular risk reduction.[23,79,126–134]

Nutrient	Youth with FH	Adults with FH	Notes
Total fatty acids	25%-30% of total daily calories	25%-35% of total daily calories	Individualize based on patient preference
Saturated fatty acids	< 7%-10% daily caloric intake	< 7%-10% daily caloric intake	Replace SFAs with UFAs to lower LDL-C
Trans fatty acids	0 g/d	0 g/d	Avoidance recommended for overall cardiovascular health
Unsaturated fatty acids (MUFAs and PUFAs)	18%-23% daily caloric intake	MUFAs: 15%-20% of daily caloric intake PUFAs: 3%-10% of daily caloric intake	Replace SFAs with UFAs to lower LDL-C
Dietary cholesterol	< 200 mg/d	Limit	Encourage consumption of a healthful dietary pattern that will inherently contain relatively low amounts of dietary cholesterol and SFAs
Plant protein	Plant protein intake is not specified in the current guidelines	30 g/d plant protein	Plant protein can be used as a partial replacement for carbohydrate or animal proteins
Viscous soluble fiber	2-12 y of age: ≥6 g/d > 12 y of age: ≥12 g/d	5-10 g/d	Encourage a variety of high-fiber foods to increase the likelihood of those rich in both viscous and soluble fibers
Plant sterols/stanols	2 g/d	2 g/d	Contraindicated for individuals with sitosterolemia
Physical activity	60 min of active time daily	≥75 min vigorous-intensity physical activity per week OR ≥150 min of moderate-intensity physical activity per week	A higher amount of physical activity each week (200-300 min) may be needed to promote weight loss and weight maintenance
Body weight change	Adequate macro- and micronutrient intake to promote normal growth and development	Decrease body weight by 5%-10% in the presence of excess adiposity	There is marked variation in the LDL-C responses to weight loss; the response may be larger in younger patients (< 40 y) and blunted in older patients (≥60 y)

Abbreviations: FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids; SFAs, saturated fatty acids; UFAs, unsaturated fatty acids.

rosuvastatin 20 to 40 mg daily to achieve ≥50% LDL-C reduction as well as LDL-C goals.[79] The primary goal is to achieve specified LDL-C goals, and the secondary goal is > 50% LDL-C lowering. The LDL-C–lowering efficacy of statins is generally consistent with expectations for individuals with HeFH but substantially diminished in individuals with HoFH (see Homozygous FH section). Moreover, most individuals with FH require additional LDL-C–lowering therapy beyond statins in order to achieve LDL-C goals.

Statins are generally very well-tolerated. However, a small percentage of patients experience statin intolerance with a variety of symptoms, most commonly statin-associated muscle symptoms.[136,137] Several strategies can be used in patients unable to tolerate high-intensity statin therapy, including changing the statin, using lower doses of statin, and less than daily statin dosing.[137] Even low-dose statin therapy is preferable to complete discontinuation.

Combination LDL-C–lowering therapy

For many patients with FH, high-intensity statin treatment is insufficient to produce the desired LDL-C reduction. Early initiation of multidrug pharmacotherapy is often necessary, similar to the management of hypertension or diabetes mellitus, with LDL-C treatment levels determining the need for combination therapy.

Contemporary nonstatin LDL-C–lowering therapy

Ezetimibe is generally the first lipid-lowering agent to be added in combination with statin treatment. It is dosed at 10 mg orally once daily and is an inexpensive, safe, and well-tolerated generic medication. Treatment with ezetimibe produces an additional 18% to 25% LDL-C lowering, with less effect in HoFH. Its efficacy in ASCVD risk reduction was demonstrated in a large cardiovascular outcome trial.[138] The medication is very well-tolerated; musculoskeletal pain and gastrointestinal distress, such as abdominal cramping and/or diarrhea, as well as minimal drug-drug interactions, are rarely reported.

PCSK9 inhibitors are appropriate as second or third-line LLTs. There are several key differences among PCSK9 inhibitors (Table 11). Multiple therapeutic PCSK9 inhibitor modalities are currently available: (1) monoclonal antibodies (alirocumab and evolocumab) that work extracellularly to sequester the PCSK9 protein in plasma; (2) inclisiran, a small interfering RNA (siRNA)-based gene-

Table 9. LDL-C–lowering medications.

Medication class	Specific agents	Dosing	Safety considerations	Contraindications
HMG–CoA reductase inhibitors (ie, statins)	Atorvastatin Fluvastatin Lovastatin Pravastatin Pitavastatin Rosuvastatin Simvastatin	Oral; once or twice daily (off-label intermittent dosing for patients to mitigate myalgia)	• Muscle-related symptoms • New onset type 2 diabetes in patients with diabetes risk factors	Acute liver failure or decompensated cirrhosis
Cholesterol absorption inhibitor	Ezetimibe	Oral; once daily	• Usually well-tolerated; mild gastrointestinal side effects and muscle complaints	Prior hypersensitivity to ezetimibe
PCSK9 inhibitor: monoclonal antibody	Alirocumab Evolocumab	Subcutaneous; every 2-4 wk (self-administered)	• Injection site reactions • Available data are insufficient to establish safety in pregnancy • Monoclonal antibodies cross the placenta	Prior hypersensitivity to the PCSK9 monoclonal antibody
PCSK9 inhibitor: siRNA	Inclisiran	Subcutaneous; at month 0, 3, then every 6 mo (clinician-administered)	• Injection site reaction • Available data are insufficient to establish safety in pregnancy	None
PCSK9 inhibitor: adnectin-based recombinant fusion protein	Lerodalcibep	Subcutaneous every month	• Injection site reactions; insufficient data to establish safety in pregnancy	None
ATP citrate lyase inhibitor	Bempedoic acid	Oral; once daily	• Hyperuricemia • Based on the mechanism of action, it may cause fetal harm	The use of bempedoic acid with pravastatin over 40 mg/day and simvastatin over 20 mg/day is to be avoided
Bile acid sequestrants	Cholestyramine Colesevelam Colestipol	Oral; once or twice daily	• Abdominal pain, bloating, dyspepsia, nausea, constipation • May be used in pregnancy	Not recommended if triglycerides > 300 mg/dL); history of hypertriglyceridemia-induced pancreatitis; bowel obstruction
Microsomal triglyceride transfer protein inhibitor	Lomitapide	Oral; once daily	• Diarrhea, nausea, vomiting, dyspepsia, and abdominal pain are common • Elevated hepatic transaminases • Increased hepatic fat • Embryo-fetal toxicity • REMS program	Pregnancy, concomitant use with a CYP3A4 inhibitor, moderate or severe hepatic impairment, or active liver disease, including unexplained persistent abnormal liver function tests
ANGPTL3 monoclonal antibody	Evinacumab	Intravenous; once monthly	• Serious hypersensitivity reactions • Embryo-fetal toxicity based on animal studies	History of serious hypersensitivity reactions to evinacumab-dgnb or to any of its excipients

Abbreviations: ANGPTL3, angiopoietin-like 3; CYP3A4, cytochrome P450 3A4; HMG-CoA, hydroxymethylglutaryl coenzyme A; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; REMS, Risk Evaluation and Mitigation Strategy; siRNA, small interfering RNA.

Table 10. Expected LDL-C reduction with LDL-C–lowering medications.

Medication class	Specific agents	Expected reduction of LDL-C in HeFH	Expected reduction of LDL-C in HoFH
HMG–CoA reductase inhibitors (statins) • High-intensity regimen[a]	Atorvastatin Rosuvastatin	≥50%	< 25%-30%
HMG–CoA reductase inhibitors (statins) • Moderate-intensity regimen[b]	Atorvastatin Rosuvastatin Simvastatin Lovastatin Pravastatin Fluvastatin	30%-49%	< 10%
Cholesterol absorption inhibitor	Ezetimibe	18%-25%	
PCSK9 inhibitor: monoclonal antibodies	Alirocumab Evolocumab	45%-64%	0%-30%
PCSK9 inhibitor: siRNA	Inclisiran	48%-52%	Minimal[152]
PCSK9 inhibitor: adnectin-based recombinant fusion protein	Lerodalcibep	59%-65%	0%-30%[144]
ATP citrate lyase inhibitor	Bempedoic acid	21%[c]	Data limited[d]
Bile acid sequestrants	Cholestyramine Colestipol Colesevelam	10%-27%	< 10%
Microsomal triglyceride transfer protein inhibitor (HoFH only)	Lomitapide	NA	40%-50%
ANGPTL3 monoclonal antibody (HoFH only)	Evinacumab	NA	49%

Abbreviations: ANGPTL3, angiopoietin-like 3; HeFH, heterozygous familial hypercholesterolemia; HMG–CoA, hydroxymethylglutaryl coenzyme A; HoFH, homozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; siRNA, small interfering RNA.

[a]Atorvastatin 40-80 mg daily, rosuvastatin 20-40 mg daily.

[b]Atorvastatin 10-20 mg, rosuvastatin 5-10 mg, simvastatin 20-40 mg, pravastatin 40-80 mg, lovastatin 40 mg, fluvastatin 80 mg, pitavastatin 2-4 mg.

[c]Greater LDL-C lowering with no or low-dose statin therapy.

[d]Normal LDL-C lowering in an uncontrolled study of 4 patients.[146]

silencing technology that inhibits mRNA translation and intracellular production of PCSK9 by the liver; and (3) lerodalcibep, a third-generation PCSK9 inhibitor, which is a recombinant fusion protein containing human albumin complexed with adnectin (the engineered adnectin moiety of the fusion protein binds PCSK9 in the bloodstream). Enlicitide decanoate is an oral PCSK9 inhibitor that lowered LDL-C by 58.2% in patients with HeFH, with FDA approval pending.[139]

These agents reduce plasma concentrations of free PCSK9, resulting in increased hepatic LDLR density and greater LDL-C–lowering capacity. The PCSK9 inhibitor drugs are potent LDL-C–lowering parenteral agents (approximately 48%-64% LDL-C lowering) and are well-tolerated. The PCSK9-inhibiting monoclonal antibodies, alirocumab and evolocumab, are proven to reduce ASCVD events in high-risk secondary prevention patients with both acute (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab; ODYSSEY OUTCOMES) and stable (FOURIER) history of ASCVD, as well as in high-risk primary prevention patients (VESALIUS-CV).[116,117,140] Inclisiran is currently under evaluation for ASCVD event reduction in 2 phase 3 trials (Inclisiran for Participants With Atherosclerotic Cardiovascular Disease, ORION-4; and Inclisiran for Secondary Prevention in Patients With Preexisting ASCVD, VICTORION-2P), among patients with preexisting ASCVD.[141] Lerodalcibep was approved in December 2025 to reduce LDL-C in adults with hypercholesterolemia, including HeFH,[142] and has been shown to lower LDL-C by 59% to 65% among patients with HeFH.[143] In patients with HoFH, lerodalcibep lowered LDL-C by a mean of 9.1% compared with 10.8% with evolocumab in a crossover study.[144]

Bempedoic acid is an oral cholesterol-lowering agent, approved by the U.S. FDA in 2020. Bempedoic acid is dosed as 180 mg orally once daily. A combination product with ezetimibe (bempedoic acid 180 mg + ezetimibe 10 mg) is also available. Bempedoic acid is FDA-approved for use in HeFH and provides a similar degree of LDL-C lowering compared with its use in patients who do not have HeFH (approximately 21% as monotherapy).[145] When used as a combination product with ezetimibe, the LDL-C reduction is approximately 40%. The results of an open-label study of bempedoic acid in 4 patients with HoFH demonstrated a mean 33% LDL-C lowering.[146]

Bempedoic acid reduced MACE in Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen, Outcomes Trial (CLEAR OUTCOMES), a large cardiovascular outcomes trial involving nearly 14,000 statin-intolerant patients with established cardiovascular disease or at high risk for cardiovascular disease.[147]

Table 11. Comparison of PCSK9 inhibitors.

	siRNA	Monoclonal antibodies	Adnectin-based recombinant fusion protein
Agent(s)	Inclisiran	Alirocumab, Evolocumab	Lerodalcibep
Mechanism of action	Inhibits PCSK9 production	Sequesters PCSK9 and inhibits binding to LDLR	Binds to the PCSK9 protein in the bloodstream
Location of action	Intracellular	Extracellular	Extracellular
Plasma level of free PCSK9	Decreases	Decreases	Decreases
LDL-C reduction in HeFH	~50%	~50%-60%	~59-65%
LDL-C reduction in HoFH	0%	0%-30%	0%-30%
Lp(a) reduction	~17%-25%	~25%-30%	~24%
Delivery method (person, site)	Healthcare clinician, clinic	Patient, home	Patient, home
Dosing	284 mg SUBQ injection on day 1, 90, then every 6 mo thereafter	Alirocumab: 75-150 mg SUBQ injection every 2 wk 300 mg SUBQ injection every 4 wk Evolocumab: 140 mg SUBQ injection every 2 wk	300 mg SUBQ injection every month
Injection volume (administration duration)	1.5 mL (5-10 s)	1 mL (8-10 s)	1.5 mL
Storage requirements	Room temperature Do not freeze	Refrigerate Stable at room temperature x 30 d Do not freeze	Refrigerate Stable at room temperature up to 3 months in the original carton Do not freeze
Key adverse effects	Injection site reactions	Injection site reactions	Injection site reactions
MACE reduction	TBD	Yes	TBD
Mortality reduction	TBD	Yes[a]	TBD
How billed	Medical benefit	Pharmacy benefit	TBD
Estimated annual drug cost[b]	US $5520-8280[c]	US $5850[c]	TBD[c]

Abbreviations: HeFH, heterozygous familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; Lp(a), lipoprotein(a); MACE, major adverse cardiovascular event; PCSK9, proprotein convertase subtilisin/kexin type 9 inhibitor; siRNA, small interfering ribonucleic acid; SUBQ, subcutaneous; TBD, to be determined.

[a]Seen in ODDESSY-Outcomes, nominally significant.

[b]Not the out-of-pocket cost to the patient for inclisiran, alirocumab, and evolocumab.

[c]Estimated cost based on 2025 Wholesale Acquisition Cost (WAC) pricing; subject to change.

Overall, bempedoic acid is well-tolerated with small increases in biomarkers such as serum creatinine, blood urea nitrogen, hemoglobin, aminotransaminases, and uric acid, and low rates of clinical events such as gout and cholelithiasis. Bempedoic acid has no physiological activity within myocytes, and randomized clinical trials have reported no difference in myalgia rates compared with placebo. However, in clinical practice, musculoskeletal adverse effects are frequently reported (without causality) and represent the primary reason for discontinuation of bempedoic acid among patients with a history of statin intolerance.[148]

Historical nonstatin LDL-C–lowering therapy

Bile acid sequestrants (cholestyramine, colestipol, colesevelam) are niche LLTs in the contemporary management of FH but may have a role in patients with FH who have a severe LDL-C elevation, drug intolerance, and/or pregnancy/breastfeeding (see below). Bile acid sequestrants can produce modest LDL-C reductions (10%-27%) in the general population and HeFH, but substantially less (< 10%) in HoFH. Additionally, bile acid sequestrants have the added benefit of a modest (~0.5%) hemoglobin A1C–lowering effect when used in patients with type 2 diabetes and may therefore be useful for individuals with FH and diabetes. Their clinical use is limited by high pill/dose burden; drug–drug interactions requiring separating administration from other medications by at least 4 hours due to binding interactions, gastrointestinal distress (abdominal pain, constipation, bloating, and nausea), and exacerbation of hypertriglyceridemia (not recommended if triglycerides of ≥300 mg/dL).[23]

Niacin, a water-soluble vitamin that has been used for decades as LLT, was proven to prevent ASCVD events in

men with ASCVD in the Coronary Drug Project, but failed to demonstrate additional cardiovascular event reduction beyond statin monotherapy in 2 large-scale cardiovascular outcome trials (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes, AIM-HIGH; and Heart Protection Study 2 – Treatment of HDL to Reduce the Incidence of Vascular Events, HPS2-THRIVE) designed to assess the benefits of increasing HDL-C on ASCVD events (not LDL-C lowering). Additionally, niacin possesses several off-target effects resulting in poor tolerability, including flushing, gastrointestinal distress (contraindicated in peptic ulcer disease), gout, hyperglycemia, hepatotoxicity (contraindicated in active hepatic disease or persistent liver transaminase elevation), and hematological effects such as thrombocytopenia (contraindicated in arterial hemorrhage). Because of these safety concerns and the availability of several other, more proven, potent, and safer agents, niacin is now rarely used. In fact, no niacin preparations approved by the European Medicines Agency (EMA) are available in Europe.[23]

Probucol, available in Japan for FH and shown to lower LDL-C by 14% to 29%, has demonstrated potential benefits in slowing the progression of carotid artery intima-media thickness but failed to prevent progression of peripheral arterial disease in the Probucol Quantitative Regression Swedish Trial (PQRST). The results of another trial showed no cardiovascular benefit.[149–151] Probucol is not commonly used outside of Japan due to concerns about lowering HDL-C and prolonging the QT interval, which led to its market removal in many regions. Given global travel, clinicians outside of Japan may still encounter patients taking this medication.

Other LLT

Fibrates (eg, gemfibrozil, fenofibrate, clofibrate—discontinued in the United States) and omega-3 fatty acids are predominantly triglyceride-lowering agents. Although the omega-3 fatty acid icosapent ethyl demonstrated cardiovascular risk reduction in select high-risk populations, omega-3 fatty acids generally have no role in FH management absent severe hypertriglyceridemia or ASCVD, as they do not modulate LDL-C clearance.

Treatment of HoFH

HoFH is the most severe form of FH and the most difficult to treat. Treatment should be initiated as soon as patients are diagnosed, regardless of their age. The presence of pathogenic biallelic variants in any of the genes that are involved in the LDLR pathway makes patients with HoFH less responsive to lipid-lowering medications that have a mechanism of action involving direct or indirect upregulation of the LDLR. These include conventional drugs, such as statins, ezetimibe, and bile acid sequestrants, as well as more recent ones, such as bempedoic acid and those targeting PCSK9. The LDL-C–lowering response to these treatments depends on the degree of residual LDLR functionality of the individual patient and is the result not only of the specific FH-causing variants carried by the patients but also of other genetic factors. This variability is demonstrated by differing responses to PCSK9 inhibition among patients carrying the same *LDLR* pathogenic variant.[153]

Lipid-lowering treatment in patients with HoFH should be initiated promptly upon diagnosis and follow a rapid stepwise intensification to multidrug treatment with the goal of achieving LDL-C targets established for patients with HoFH (Fig 2).

The initial treatment step should include the simultaneous initiation of high-potency statins and ezetimibe. Lipid levels should be assessed 1 to 2 months after the start of treatment. If target LDL-C levels are not achieved, which is the typical situation, treatment should be escalated to include a PCSK9 inhibitor monoclonal antibody at a dose that is appropriate and approved for HoFH. If the response to treatment is absent or minimal after 1 to 2 doses (≤15%), discontinuation of the PCSK9 inhibitor could be considered, and other lipid-lowering treatments initiated. However, full LDL-C–lowering effects may be delayed for a few months in some patients, and treatment could be continued if there is a 10% to 15% reduction of LDL-C. Of note, inclisiran seems to have only a minimal, if any, effect on lowering LDL-C in patients with HoFH.[152]

Most, if not all, patients with HoFH will have an inadequate response to this triple combination therapy and are likely to require the addition of 1 or more LDLR-independent treatments, ie, treatments with a mechanism of action that is independent of the degree of LDLR functionality. These include lomitapide, evinacumab, and lipoprotein apheresis. Liver transplantation may be considered in selected pediatric cases, but this is not commonly done.

Lomitapide

Lomitapide is an inhibitor of microsomal triglyceride transfer protein, a key protein involved in the lipidation of apo B and the production of apo B–containing lipoproteins, including very low-density lipoprotein (VLDL) (the precursor of LDL) and chylomicrons. As its mechanism of action is not dependent on the presence of residual LDLR functionality, it is an efficacious lipid-lowering treatment for HoFH. LDL-C levels decrease by 50% at a mean dose of 40 mg/d,[154] with sustained efficacy shown over a 5-year follow-up.[155] Similar reductions in LDL-C have been shown in real-world settings with lower doses of lomitapide.[156]

The most common adverse events seen with lomitapide use are mild to moderate gastrointestinal symptoms and increased hepatic fat, as well as intestinal steatosis, both expected based on its mechanism of action.[154] To minimize gastrointestinal symptomatology and maximize tolerability, its administration includes a gradual up-titration and must be accompanied by adherence to a low-fat diet (less than

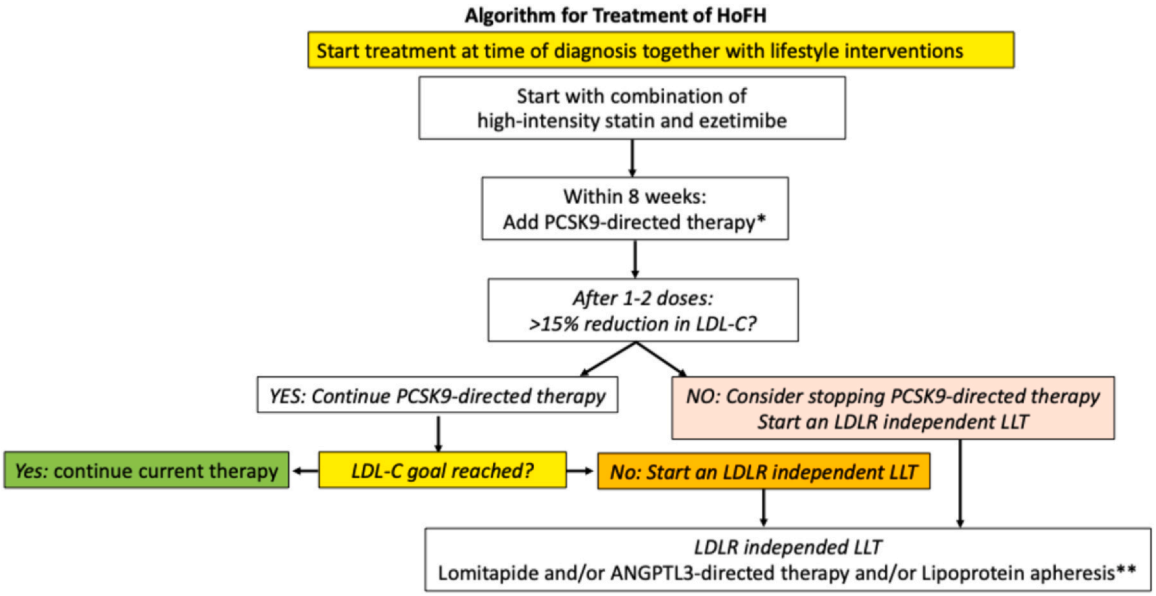

Figure 2. Algorithm for treatment of patients with homozygous familial hypercholesterolemia. *If PCSK9 inhibitors are not available or accessible, then consider lipoprotein apheresis. **Any of the LDLR-independent LLT can be considered based on availability and considerations that are assessed during a clinician/patient conversation. A combination of these may be considered if LDL-C goals are not reached when only 1 of them is added to the LLT regimen. Abbreviations: ANGPTL3, angiopoietin-like 3; HoFH, homozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; LLT, lipid-lowering therapy; PCSK9, proprotein convertase subtilisin/kexin type 9.

10%-20% of energy from fat), supplementation with vitamin E and essential fatty acids, and alcohol restriction. Regular liver function testing is needed before starting the treatment, at the time of up-titration, and regularly during dose maintenance.

Current data available from clinical trials and real-world studies support the tolerability and safety of lomitapide over several years of treatment.[155–158] However, because of the uncertain long-term risk associated with hepatic steatosis, this drug is available in the United States only through a Risk Evaluation and Mitigation Strategy (REMS) program.[159]

A small real-world study in patients treated with lomitapide reported regression or stabilization of carotid intima-media thickness over a 4- to 5-year follow-up period.[160] A trend towards MACE reduction was also observed in the Pan-European study.[156]

Although its efficacy and safety have been reported in a recent pediatric clinical trial in children as young as 5 years,[161] it is approved by the FDA only for individuals ≥18 years.

Evinacumab

Evinacumab is a monoclonal antibody against ANGPTL3, a key inhibitor of 2 lipases, lipoprotein lipase and endothelial lipase. The inhibition of ANGPTL3 results in an increased activity of both lipoprotein lipase and endothelial lipase. Treatment with evinacumab at a dose of 15 mg/kg, administered as a 1-hour infusion every 4 weeks, results in an approximate 50% reduction in LDL-C in individuals with HoFH.[162,163] Although the mechanism underlying the reduction in LDL-C is mediated in part by increases in endothelial lipase, the full mechanism is not yet completely understood. Importantly, it is independent of the presence of residual LDLR activity, as the overall lipid-lowering effect is similar in patients with HoFH who carry *LDLR* defective and null pathogenic variants.[162]

It is generally well-tolerated and was approved by the FDA for patients 1 year and older[169], an expansion from the previous indication for those aged 5 years and older.[164,165] Case reports have described treatment with evinacumab in children as young as 6 months of age,[166,167] and the EMA approved the indication of evinacumab for HoFH aged 6 months and older.[168]

No long-term data on ASCVD outcomes are available, but the results of Mendelian randomization studies suggest a probable benefit. A country-specific, real-world data analysis in a cohort of patients with HoFH treated with evinacumab for 3.5 years showed no cardiovascular disease events during this period, compared with 24% of patients experiencing cardiovascular disease events over 4 years in the control cohort.[170] Plaque regression was seen in 2 patients with severe HoFH treated with evinacumab.[115]

Lipoprotein apheresis

Lipoprotein apheresis is an important therapeutic intervention that is needed for < 1% to 2% of patients with HeFH, but a much larger proportion of patients with HoFH.[171]

Lipoprotein apheresis using the Liposorber system (Kaneka) (the only device available in the United States) involves the extracorporeal removal of apo B–containing

lipoproteins, including LDL, VLDL, remnant lipoproteins, and Lp(a), from plasma during a procedure that lasts 3 to 4 hours.[172] With this system, venous blood is passed through a column that separates plasma from red blood cells, leukocytes, and platelets, allowing plasma to be passed through a second column in which negatively charged dextran sulfate binds to positive charges on apo B in lipoproteins. Apo B–depleted plasma is mixed with cellular components from blood and reinfused into the patient through a second intravenous catheter. During a single lipoprotein apheresis treatment, the LDL-C and Lp(a) concentrations are decreased acutely by 75% to 85% and 65% to 75%, respectively, with time-averaged reductions of 23% to 50% and 20% to 40%, respectively.[172] Treatment is often repeated every 2 weeks in patients with HeFH and weekly in patients with HoFH. Patients should not be taking an angiotensin-converting enzyme inhibitor due to the possibility of developing severe hypotension.

Lipoprotein apheresis has been safely used in children with HoFH as young as 2 years. A minimum body weight of 15 kg is recommended because of the large extracorporeal blood volume (approximately 400 mL) required for this procedure.

The benefits of lipoprotein apheresis beyond LDL-C and Lp(a) lowering include acute reductions in markers of inflammation, such as high-sensitivity C-reactive protein; improved endothelial function and increased cardiac microvascular flow reserve; decreased fibrinogen and procoagulant factors; decreased blood viscosity; and improvement in clinical symptoms, such as angina and exercise tolerance. Data from mostly observational trials indicate that lipoprotein apheresis treatment appears to reduce the incidence of ASCVD events, although confirmation from randomized controlled trials is lacking.[172]

The indications for lipoprotein apheresis have evolved substantially over the last 28 years since initial FDA approval. The recently updated indications from January 2025 are shown in Table 12.

Liver transplantation for HoFH

Liver transplantation is considered a treatment of last resort for children with HoFH who experience rapidly progressive cardiovascular disease despite maximum LLT and failure to achieve LDL-C goals.[25] This includes patients with poor drug response due to biallelic null variants, drug intolerance, or lack of access to required therapies. Severely affected children may be younger than the approved age of use of other therapies. In the presence of terminal cardiac failure, combined liver/heart transplantation may be considered.[173]

When transplanted with a normal liver, LDL-C levels rapidly decrease and remain low in most reported cases.[174–176] Skin xanthomas flatten, and Lp(a) levels also improve,[177,178] but will reflect Lp(a) levels in the donor.

Waiting lists are usually short for children, and the short- and long-term risks of surgery and immunosuppression have decreased.[179,180] Regression of coronary artery disease and possibly aortic valve stenosis may occur,[177,181–183] but progression of aortic valve disease has also been reported.[177,184] Hence, more data on cardiovascular outcomes after liver transplantation for HoFH are needed. Success will vary depending on the timing of transplantation, surgical expertise, comorbidities, and patient adherence to and success with immunosuppressive therapy.

Considerations for treatment in children with FH

LLT is generally well-tolerated in children and adolescents with FH. However, many pediatricians are hesitant to prescribe these medications, which can lead to delays in necessary therapy. Even when pediatric clinicians are comfortable prescribing, parents may express concerns about when to start treatment for their children with HeFH. Additionally, maintaining medication adherence can be difficult, especially for adolescents living at home or young adults attending college.

- Statins are approved for treatment in children with HeFH beginning at 8 to 10 years in the United States. Some clinicians start earlier, at age 6 years, in children with family histories of early-onset ASCVD events or other significant risk factors.
- Ezetimibe is approved from age 10 years for HeFH and age 9 years for HoFH, but clinicians treating HoFH use it earlier.
- Evolocumab is approved for HeFH and HoFH for children aged 10 years and older. Alirocumab is approved

Table 12. Indications for lipoprotein apheresis in the United States.

	Diagnosis[a]	Lipoprotein level[b]	Presence of ASCVD required
Group A	HoFH	LDL-C ≥500 mg/dL	No
Group B	HeFH	LDL-C ≥300 mg/dL	No
Group C	HeFH	LDL-C ≥70 mg/dL	Documented CAD or PAD
Group D	HeFH	Lp(a) ≥60 mg/dL or > 130 nmol/L	Documented CAD or PAD

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; HeFH, heterozygous familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); PAD, peripheral artery disease.

[a]Clinically diagnosed.

[b]On maximally tolerated lipid-lowering therapy.

for children aged 8 years and older with HeFH and HoFH, but both are used earlier in children with HoFH.
- Bempedoic acid is not approved for use in children.
- Evinacumab is approved for HoFH children aged 1 and older.

Lipoprotein(a)

Lp(a) contributes to the increased risk of ASCVD in patients with FH. The NLA update on Lp(a) recommended assessment at least once in all adults.[185] All patients with FH, including children and adolescents, should also have Lp(a) measured.

Update on treatment of HeFH and HoFH in pregnancy

Women with FH often experience prolonged interruptions in LLT during their reproductive years—2 years (median) and 14 years (maximum) per published data.[186] These off-treatment periods leave women vulnerable to ASCVD risk and events,[186] making it vital that clinicians be well versed in the indications and contraindications to pharmacologic therapy during pregnancy and breastfeeding. Individualized counseling and shared decision-making regarding lipid management are crucial for individuals with FH who are pregnant or planning pregnancy, and management by an interdisciplinary team with expertise in FH, including lipid specialists, should be considered before pregnancy.[187]

Although statins are a cornerstone treatment for FH, their use has generally been avoided during pregnancy due to concerns based on limited data.[188] However, in 2021, the FDA removed its strongest label warning against statins during pregnancy, allowing more flexibility for high-risk women with HoFH or severe HeFH.[189] Ongoing clinical studies are investigating the potential use and safety of pravastatin for preeclampsia prevention among pregnant women.[190–193] Thus, prolonged statin washout periods for individuals planning pregnancy is not necessary, and statin use could be considered up to conception. However, statins should not be used during breastfeeding since they may be excreted in breast milk.[189]

Bile acid sequestrants are considered safe during pregnancy and breastfeeding due to minimal systemic absorption and may be used in patients with FH, although efficacy may be limited.

Most other LLTs—ezetimibe, PCSK9 inhibitors, and bempedoic acid—lack safety data for pregnancy and breastfeeding. Therefore, their use is not advised during pregnancy and breastfeeding.[187]

Lipoprotein apheresis appears to be safe and effective for LDL-C lowering during pregnancy, reducing time-averaged LDL-C by 25% to 30%.[194,195] It is particularly important in HoFH, as cholesterol levels typically rise significantly during pregnancy, sometimes associated with fatal and nonfatal myocardial infarction during pregnancy.[196,197] Lipoprotein apheresis should be discussed as a potential option during preconception planning and during pregnancy for women with HoFH.

Health disparities

Disparities in FH care are prevalent and contribute to worse ASCVD outcomes. Women with FH are consistently undertreated, receiving high-intensity statin therapy less often than men and attaining LDL-C goals less frequently.[198–200] Black and Asian patients with FH are less likely to achieve LDL-C goals compared with their White counterparts.[201] Furthermore, socioeconomic barriers limit access to lipid specialists and advanced LLT.[202] Globally, access to adequate LLT is very limited in many countries, severely compromising care for patients with severe HeFH and HoFH.

Economic impact of FH

Approximately 1.4 million people in the United States and 34 million worldwide have FH. Yet the majority remain undiagnosed, especially at younger ages.[203] Annually, about 140,000 of the 3.5 million births in the United States are expected to have HeFH, and without treatment, roughly 40,000 of these will experience a cardiovascular event by age 40 years. The potential to prevent ASCVD events is substantial.

For individuals diagnosed with FH in *mid-life or* later (eg, >50 years), aggressive LLT is cost-effective across various societal willingness-to-pay (WTP) thresholds. In this population, a payer perspective often serves as a proxy for a societal one, assuming minimal nonmedical costs. If productivity cost (eg, lost income) are included, the cost-effectiveness of therapy becomes even more favorable.[204]

Cost-effectiveness analysis (CEA) for FH in *children and young adults*, however, is more complex with potentially greater societal impact.[205] Evaluating the cost-effectiveness of genetic testing and lifelong LLT is challenging due to the long time horizon (approximately 70 years). As such, a 30-year time horizon might be considered. Untreated 10-year-olds with FH face a significant risk of death (around 10%) or myocardial infarction (around 20%) by age 40 years,[118] - risks largely mitigated with LLT. For individuals with FH experiencing cardiovascular events or death in their 30s or mid-life, the personal and economic impact on their families is substantial, making a payer perspective inadequate due to significant indirect costs like lost productivity. Given these uncertainties, U.S.-based CEA studies on genetic testing for FH in children and young adults have been limited in providing definitive cost-effectiveness estimates. Genetic diagnosis and appropriate therapy for FH are likely to be cost-effective at any WTP threshold.[206] In some analyses, this approach may represent a dominant strategy offering both improved health outcomes and lower overall costs.

Cascade screening of FH families is essential to improve the rate of diagnosis of FH in the United States. While the optimal implementation of widespread cascade screening and its full economic consequences are still being investigated, evidence suggests that genetic diagnosis and appropriate therapy are likely to fall within societal WTP thresholds. This supports the economic justification for a societal program of cascade screening. Further research will refine our understanding of the economic impact of FH.

Given the inherent uncertainties and limitations of CEAs, these studies should inform, rather than dictate, health policy decisions.

Patient perspective

1) *In a nutshell, what would be your "ideal" for people getting diagnosed?*
   As someone who lives with HoFH, my ideal scenario would be for newborn screening for HoFH for everyone. It is an easy test, and it would catch the majority of patients with HoFH (and sometimes their parents as well). For those of us living with HoFH, the earlier we can be diagnosed and treated, the better. More medications and treatments are becoming approved for younger children, so any young children identified could be treated. The best-case scenario would be that a child with HoFH is treated and managed from birth, thereby avoiding heart disease, heart damage, xanthomas, and other effects of HoFH.
   For individuals who have FH, but not HoFH, the ideal in my mind would be testing no later than age 8 for all children, and by age 5 for anyone with a (family) history of ASCVD. Again, earlier treatment leads to better outcomes, and from my personal experience (my brother and sister both have FH as well), if you start on medications younger, it is more likely to become part of your "normal" routine, and therefore easier to build a habit of compliance early in life that benefits you as you age.
2) *What should a practicing clinician know about FH from your viewpoint?*
   With FH, we cannot "eat ourselves" to the LDL cholesterol levels we have, so keep that in mind when determining a treatment path. Asking individuals to track food intake, meet with a nutritionist, etc, can delay treatment when diet and exercise modification likely won't have much of an impact on people with FH. Diet and exercise are, of course, always important for everyone but will not be a "cure" for FH. In my experience, sometimes a clinician would think that I must not have fasted before bloodwork, or that I was misrepresenting my diet when they saw my labs, so I would also encourage clinicians to believe their patients!
   Early intervention is crucial with FH, and especially with HoFH, so when children or young people are diagnosed, do not wait for treatment until "after puberty," or tell women to think about treatment when they are done having children. I have heard so many stories of people being told to wait, that the risk is not until later in life, and that is just not true. The earlier the LDL levels can be brought down, the better.
   Additionally, FH is a risk for women and children, not just for men. Heart disease may be more common in men in general, but everyone with FH is at risk, regardless of age, race, gender, etc. So, all patients with FH should be treated early and aggressively.
   Finally, I would say to understand that sometimes there is also a level of guilt associated with passing along a genetic condition to children, so be sensitive to that when talking with parents and family members. Even though it is not anyone's fault, I know it was very difficult for my father when I had my first bypass and my heart attack. He felt a lot of responsibility, and it was really hard for him to be the caregiver instead of the patient.
3) *What would have helped you along your journey, and how has the lack of FH knowledge in clinicians impacted your health?*
   I have moved a lot during my adult life due to my husband's job, so I have changed clinicians more often than many people, I would imagine. And each time, I felt like I was starting over, having to explain my condition, tell the doctor that diet changes were not going to make a difference, reasserting that I did need statins and medications (some wanted to take me off of medications to see what my LDL would be), and asking for specific tests or follow-up. I have always had to advocate for myself to ensure I got adequate care. This kind of patient responsibility carries with it not just the risk of treatment disruption, but also personal stress in trying to manage my own records and advocating for my care.
   On top of this is the insurance side, which can be very stressful. The onus has been on me to ensure necessary medications and tests are fully covered before tests are done or medications are administered. It is very expensive when they are not preapproved, and it can be difficult to get all of the information the insurance company needs. One of the first things I ask a new doctor is if his/her staff is able to work with a difficult insurance company and help me with referrals and authorization paperwork. There is a significant burden on me as the patient to stay on top of insurance requirements, coordinate between clinicians and insurance, renew referrals, etc.
   This burden actually had a very direct impact on me, because during a care clinician transition in 2010 to 2011, I was meeting with a new doctor, explaining why I was doing apheresis, and then talking to my insurance company about why I needed apheresis (again, despite having been on it for about 8 years at the time). During this transition in care, I was unable to get apheresis for about 3 months, awaiting approvals and navigating back and forth, and it was during this time that I had a heart attack. I do feel that if my clinician had a better

understanding of HoFH, he would have put in more effort to get the approval process moving and would not have let me go so long between treatments.

Advocating for myself also meant asking my clinician about new or different treatments. I would have to bring up specific medications that I had heard about on the news or in commercials if I were not on those drugs and push to be put on them. I do think I could have been more aggressively treated at certain times in my life, and the responsibility for finding new treatments should not have been on me as the patient.

I want to be clear that my clinicians were well-intentioned and responsive to my requests, so I do not believe they were being negligent or "bad doctors." It was simply that they did not know enough about FH or HoFH to be the true driver of my care.

4) *What have you learned through the whole process of your health journey, and how would you like to educate clinicians to make the process go differently?*

As I said above, I have learned to be my own advocate, and I think that is something all patients should be. I should be educated about my condition and aware of new treatments. But I think I would have been treated earlier and more aggressively if my doctors themselves had known more about FH, and I would not have had to "start over" every time I went to a new doctor, going back to step 1 each time in developing a treatment plan. I would like to see FH be something all clinicians are aware of, beginning in medical school. I'd like to see all doctors be knowledgeable about FH and take it as seriously as they do things like diabetes, cystic fibrosis, or asthma. Given the rate of occurrence in the United States, I think FH is something that primary care doctors and pediatricians should know about, and not just cardiologists. Additionally, endocrinologists, gynecologists, ophthalmologists, dermatologists, hematologists, vascular doctors, and others should also be aware, because patients with FH can come in with symptoms that could take them to any one of these doctors. In addition to medical school and specialty training, I would imagine continuing medical education courses, conferences, and publications would be other good ways for clinicians to learn more about FH.

Research gaps and future directions

- Although there has been significant progress in the last decade, HoFH remains a very difficult condition to treat. The development of novel therapeutic approaches, including gene transfer and gene editing, is in early development.
- Severe aortic valve stenosis is common in HoFH, including in children, where it can be the first clinical manifestation. Aggressive LLT does not seem to alter its progression. More research is needed to understand its pathophysiology and to identify nonsurgical therapeutic approaches.
- The development of a valid neonatal screening test for FH performed in all births as part of the existing standard screening would greatly expand the identification and early intervention for this disorder.
- More research is needed into the dissemination of information about FH and in the implementation of strategies for screening and treatment.

CRediT authorship contribution statement

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Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jacl.2026.01.011.

References

1. Hu P, Dharmayat KI, Stevens CAT, et al. Prevalence of familial hypercholesterolemia among the general population and patients with atherosclerotic cardiovascular disease: a systematic review and meta-analysis. *Circulation.* 2020;141(22):1742–1759. https://doi.org/10.1161/CIRCULATIONAHA.119.044795.
2. Tromp TR, Hartgers ML, Hovingh GK, et al. Worldwide experience of homozygous familial hypercholesterolaemia: retrospective cohort study. *Lancet.* 2022;399(10326):719–728. https://doi.org/10.1016/S0140-6736(21)02001-8.
3. Goldberg AC, Hopkins PN, Toth PP, et al. 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.* 2011;5(3):S1–51. https://doi.org/10.1016/j.jacl.2011.03.001.
4. Garcia-Garcia AB, Ivorra C, Martinez-Hervas S, et al. Reduced penetrance of autosomal dominant hypercholesterolemia in a high percentage of families: importance of genetic testing in the entire family. *Atherosclerosis.* 2011;218(2):423–430. https://doi.org/10.1016/j.atherosclerosis.2011.07.106.
5. Sturm AC, Knowles JW, Gidding SS, et al. Clinical genetic testing for familial hypercholesterolemia: JACC Scientific Expert Panel. *J Am Coll Cardiol.* 2018;72(6):662–680. https://doi.org/10.1016/j.jacc.2018.05.044.
6. Haase A, Goldberg AC. Identification of people with heterozygous familial hypercholesterolemia. *Curr Opin Lipidol.* 2012;23(4):282–289. https://doi.org/10.1097/MOL.0b013e3283556c33.
7. Williams RR, Hunt SC, Schumacher MC, et al. Diagnosing heterozygous familial hypercholesterolemia using new practical criteria validated by molecular genetics. *Am J Cardiol.* 1993;72(2):171–176. https://doi.org/10.1016/0002-9149(93)90155-6.
8. Austin MA, Hutter CM, Zimmern RL, Humphries SE. Genetic causes of monogenic heterozygous familial hypercholesterolemia: a HuGE prevalence review. *Am J Epidemiol.* 2004;160(5):407–420. https://doi.org/10.1093/aje/kwh236.
9. Risk of fatal coronary disease in familial hypercholesterolaemia. Scientific Steering Committee on behalf of the Simon Broome Register Group. *BMJ.* 1991;303(6807):893–896. https://doi.org/10.1136/bmj.303.6807.893.
10. Gidding SS, Champagne MA, de Ferranti SD, et al. The agenda for familial hypercholesterolemia: a scientific statement from the American Heart Association. *Circulation.* 2015;132(22):2167–2192. https://doi.org/10.1161/cir.0000000000000297.
11. Harada-Shiba M, Arai H, Ohmura H, et al. Guidelines for the diagnosis and treatment of adult familial hypercholesterolemia 2022. *J Atheroscler Thromb.* 2023;30(5):558–586. https://doi.org/10.5551/jat.CR005.
12. McGowan MP, Hosseini Dehkordi SH, Moriarty PM, Duell PB. Diagnosis and treatment of heterozygous familial hypercholesterolemia. *J Am Heart Assoc.* 2019;8(24):e013225. https://doi.org/10.1161/JAHA.119.013225.
13. Ahmad ZS, Andersen RL, Andersen LH, et al. US physician practices for diagnosing familial hypercholesterolemia: data from the CASCADE-FH registry. *J Clin Lipidol.* 2016;10(5):1223–1229. https://doi.org/10.1016/j.jacl.2016.07.011.
14. Brinton EA, Duell PB. Achilles tendon palpation for diagnosis of familial hypercholesterolemia: the compelling need to restore a valuable lost art. *J Clin Lipidol.* 2025;19(1):7–9. https://doi.org/10.1016/j.jacl.2024.12.002.
15. Tsouli SG, Kiortsis DN, Argyropoulou MI, et al. Pathogenesis, detection and treatment of Achilles tendon xanthomas. *Eur J Clin Invest.* 2005;35(4):236–244. https://doi.org/10.1111/j.1365-2362.2005.01484.x.
16. Tada H, Nohara A, Usui S, et al. Validation of physical examinations of tendon xanthomas and changes in the cutoff values of Achilles tendon thickness on radiography in the clinical criteria of heterozygous familial hypercholesterolemia in Japan. *J Clin Lipidol.* 2024;18(5):e825–831. https://doi.org/10.1016/j.jacl.2024.06.008.
17. Winder AF, Jolleys JC, Day LB, Butowski PF. Corneal arcus, case finding and definition of individual clinical risk in heterozygous familial hypercholesterolaemia. *Clin Genet.* 1998;54(6):497–502. https://doi.org/10.1111/j.1399-0004.1998.tb03770.x.
18. Fernández A, Sorokin A, Thompson PD. Corneal arcus as coronary artery disease risk factor. *Atherosclerosis.* 2007;193(2):235–240. https://doi.org/10.1016/j.atherosclerosis.2006.08.060.
19. Jasani R, Ahmad Z, Schneider R, et al. Applying an LDL-C threshold-based approach to identify individuals with familial hypercholesterolemia. *J Clin Lipidol.* 2022;16(4):508–515. https://doi.org/10.1016/j.jacl.2022.04.001.
20. Gu J, Sanchez RJ, Koumas A, et al. Simulation model to estimate pretreatment (baseline) low-density lipoprotein cholesterol levels in people living with homozygous familial hypercholesterolemia. *J Clin Lipidol.* 2025;19(5):1457–1462. https://doi.org/10.1016/j.jacl.2025.08.011.
21. Brown EE, Sturm AC, Cuchel M, et al. Genetic testing in dyslipidemia: a scientific statement from the National Lipid Association. *J Clin Lipidol.* 2020;14(4):398–413. https://doi.org/10.1016/j.jacl.2020.04.011.
22. Wierzbicki AS, Humphries SE, Minhas R. Familial hypercholesterolaemia: summary of NICE guidance. *BMJ.* 2008;337:a1095. https://doi.org/10.1136/bmj.a1095.

23. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J.* 2020;41(1):111–188. https://doi.org/10.1093/eurheartj/ehz455.
24. Green RF, Dotson WD, Bowen S, et al. Genomics in public health: perspective from the Office of Public Health Genomics at the Centers for Disease Control and Prevention (CDC). *Healthcare.* 2015;3(3):830–837. https://doi.org/10.3390/healthcare3030830.
25. Cuchel M, Raal FJ, Hegele RA, et al. 2023 Update on European Atherosclerosis Society Consensus Statement on Homozygous Familial Hypercholesterolaemia: new treatments and clinical guidance. *Eur Heart J.* 2023;44(25):2277–2291. https://doi.org/10.1093/eurheartj/ehad197.
26. Berberich AJ, Hegele RA. The complex molecular genetics of familial hypercholesterolaemia. *Nat Rev Cardiol.* 2019;16(1):9–20. https://doi.org/10.1038/s41569-018-0052-6.
27. Watts GF, Gidding SS, Hegele RA, et al. International Atherosclerosis Society guidance for implementing best practice in the care of familial hypercholesterolaemia. *Nat Rev Cardiol.* 2023;20(12):845–869. https://doi.org/10.1038/s41569-023-00892-0.
28. Chora JR, Iacocca MA, Tichý L, et al. The Clinical Genome Resource (ClinGen) Familial Hypercholesterolemia Variant Curation Expert Panel consensus guidelines for LDLR variant classification. *Genet Med.* 2022;24(2):293–306. https://doi.org/10.1016/j.gim.2021.09.012.
29. Hegele, Borén RA, Ginsberg J, et al. Rare dyslipidaemias, from phenotype to genotype to management: a European Atherosclerosis Society task force consensus statement. *Lancet Diabetes Endocrinol.* 2020;8(1):50–67. https://doi.org/10.1016/S2213-8587(19)30264-5.
30. Di Taranto MD, Fortunato G. Genetic heterogeneity of familial hypercholesterolemia: repercussions for molecular diagnosis. *Int J Mol Sci.* 2023;24(4):3224. https://doi.org/10.3390/ijms24043224.
31. Jarauta E, Bea-Sanz AM, Marco-Benedi V, Lamiquiz-Moneo I. Genetics of hypercholesterolemia: comparison between familial hypercholesterolemia and hypercholesterolemia nonrelated to LDL receptor. *Front Genet.* 2020;11:554931. https://doi.org/10.3389/fgene.2020.554931.
32. Awan Z, Choi HY, Stitziel N, et al. APOE p.Leu167del mutation in familial hypercholesterolemia. *Atherosclerosis.* 2013;231(2):218–222. https://doi.org/10.1016/j.atherosclerosis.2013.09.007.
33. Bello-Álvarez D, Cenarro A, Bea AM, et al. APOE p.(Leu167del) variant in hypercholesterolemia: prevalence & phenotypic expression. *J Clin Lipidol.* 2025;19(6):1637–1645. https://doi.org/10.1016/j.jacl.2025.09.016.
34. Myrie SB, Steiner RD, Mymin D. Sitosterolemia. In: Adam MP, Bick S, Mirzaa GM, editors. *GeneReviews®*. University of Washington, Seattle; 2025. April 4, 2013. Updated July 16, 2020 https://www.ncbi.nlm.nih.gov/books/NBK131810/.
35. Tada MT, Rocha VZ, Lima IR, et al. Screening of ABCG5 and ABCG8 genes for sitosterolemia in a familial hypercholesterolemia cascade screening program. *Circ Genom Precis Med.* 2022;15(3):e003390. https://doi.org/10.1161/CIRCGEN.121.003390.
36. Guay SP, Paquette M, Blais C, et al. Two cases of sitosterolemia falsely diagnosed as familial hypercholesterolemia: could digging deeper have avoided harm? *JCEM Case Rep.* 2024;2(5):luae086. https://doi.org/10.1210/jcemcr/luae086.
37. Chora JR, Alves AC, Medeiros AM, et al. Lysosomal acid lipase deficiency: a hidden disease among cohorts of familial hypercholesterolemia? *J Clin Lipidol.* 2017;11(2):477–484.e2. https://doi.org/10.1016/j.jacl.2016.11.002.
38. DeBarber AE, Duell PB. Update on cerebrotendinous xanthomatosis. *Curr Opin Lipidol.* 2021;32(2):123–131. https://doi.org/10.1097/MOL.0000000000000740.
39. DeBarber AE, Schaefer EJ, Do J, et al. Genetically and clinically confirmed atypical cerebrotendinous xanthomatosis with normal cholestanol and marked elevations of bile acid precursors and bile alcohols. *J Clin Lipidol.* 2024;18(3):e465–476. https://doi.org/10.1016/j.jacl.2024.03.004.
40. Salen G, Steiner RD. Epidemiology, diagnosis, and treatment of cerebrotendinous xanthomatosis (CTX). *J Inherit Metab Dis.* 2017;40(6):771–781. https://doi.org/10.1007/s10545-017-0093-8.
41. Varughese MG, Deshotels MR, Zhang L, Ballantyne CM. Severe hypercholesterolemia in a patient with very low albumin and normal renal function. *J Clin Lipidol.* 2023;17(1):64–67. https://doi.org/10.1016/j.jacl.2022.10.011.
42. Wang J, Dron JS, Ban MR, et al. Polygenic versus monogenic causes of hypercholesterolemia ascertained clinically. *Arterioscler Thromb Vasc Biol.* 2016;36(12):2439–2445. https://doi.org/10.1161/atvbaha.116.308027.
43. Ahmad Z, Adams-Huet B, Chen C, Garg A. Low prevalence of mutations in known loci for autosomal dominant hypercholesterolemia in a multiethnic patient cohort. *Circ Cardiovasc Genet.* 2012;5(6):666–675. https://doi.org/10.1161/circgenetics.112.963587.
44. Jacob E, Hegele RA. Monogenic versus polygenic forms of hypercholesterolemia and cardiovascular risk: are there any differences? *Curr Atheroscler Rep.* 2022;24(6):419–426. https://doi.org/10.1007/s11883-022-01018-6.
45. Tabet DR, Coté AG, Lancaster MC, et al. The functional landscape of coding variation in the familial hypercholesterolemia gene *LDLR*. *Science* 2025:eady7186. https://doi.org/10.1126/science.ady7186. Epub ahead of print. PMID: 41166440; PMCID: PMC12726852.
46. Zhang Y, de Ferranti SD, Moran AE. Genetic testing for familial hypercholesterolemia. *Curr Opin Lipidol.* 2024;35(2):93–100. https://doi.org/10.1097/MOL.0000000000000925.
47. Ormond KE, Hallquist MLG, Buchanan AH, et al. Developing a conceptual, reproducible, rubric-based approach to consent and result disclosure for genetic testing by clinicians with minimal genetics background. *Genet Med.* 2019;21(3):727–735. https://doi.org/10.1038/s41436-018-0093-6.
48. Hallquist MLG, Tricou EP, Ormond KE, et al. Application of a framework to guide genetic testing communication across clinical indications. *Genome Med.* 2021;13(1):71. https://doi.org/10.1186/s13073-021-00887-x.
49. Rickman AF, Fitzgerald-Butt SM, Spoonamore KG, et al. A descriptive investigation of clinical practice models used by cardiovascular genetic counselors in North America. *J Genet Couns.* 2023;32(2):362–375. https://doi.org/10.1002/jgc4.1643.
50. Reuter C, Grove ME, Orland K, et al. Clinical cardiovascular genetic counselors take a leading role in team-based variant classification. *J Genet Couns.* 2018;27(4):751–760. https://doi.org/10.1007/s10897-017-0175-7.
51. Tromp TR, Reijman MD, Wiegman A, et al. Counseling couples at risk of having a child with homozygous familial hypercholesterolemia—clinical experience and recommendations. *J Clin Lipidol.* 2023;17(2):291–296. https://doi.org/10.1016/j.jacl.2022.12.006.
52. Wand H, Sturm AC, Erby L, et al. Genetic testing preferences and intentions in patients with clinically diagnosed familial hypercholesterolemia. *J Genet Couns.* 2020;29(6):919–927. https://doi.org/10.1002/jgc4.1194.
53. Morales A, Goehringer J, Sanoudou D. Evolving cardiovascular genetic counseling needs in the era of precision medicine. *Front Cardiovasc Med.* 2023;10:1161029. https://doi.org/10.3389/fcvm.2023.1161029.
54. Morgan KM, Campbell-Salome G, Walters NL, et al. Innovative implementation strategies for familial hypercholesterolemia cascade testing: the impact of genetic counseling. *J Pers Med.* 2024;14(8):841. https://doi.org/10.3390/jpm14080841.
55. Nomura A, Okada H, Nohara A, et al. Impact of providing genetics-based future cardiovascular risk on LDL-C in patients with familial hypercholesterolemia. *J Clin Lipidol.* 2023;17(5):622–632. https://doi.org/10.1016/j.jacl.2023.08.007.
56. Rothstein MA, Anderlik MR. What is genetic discrimination, and when and how can it be prevented? *Genet Med.* 2001;3(5):354–358. https://doi.org/10.1097/00125817-200109000-00005.

57. Rothstein MA. Can genetic nondiscrimination laws save lives? *Hastings Cent Rep.* 2021;51(1):6–7. https://doi.org/10.1002/hast.1204.
58. Green RC, Lautenbach D, McGuire AL. GINA, genetic discrimination, and genomic medicine. *N Engl J Med.* 2015;372(5):397–399. https://doi.org/10.1056/NEJMp1404776.
59. Rothstein MA, Brothers KB. Banning genetic discrimination in life insurance—time to follow Florida's lead. *N Engl J Med.* 2020;383(22):2099–2101. https://doi.org/10.1056/NEJMp2024123.
60. Joly Y, Dupras C, Pinkesz M, et al. Looking beyond GINA: policy approaches to address genetic discrimination. *Annu Rev Genomics Hum Genet.* 2020;21:491–507. https://doi.org/10.1146/annurev-genom-111119-011436.
61. Eid WE, Sapp EH, Wendt A, et al. Improving familial hypercholesterolemia diagnosis using an EMR-based hybrid diagnostic model. *J Clin Endocrinol Metab.* 2022;107(4):1078–1090. https://doi.org/10.1210/clinem/dgab873.
62. Qureshi N, Akyea RK, Dutton B, et al. Case-finding and genetic testing for familial hypercholesterolaemia in primary care. *Heart.* 2021;107(24):1956–1961. https://doi.org/10.1136/heartjnl-2021-319742.
63. Myers KD, Knowles JW, Staszak D, et al. Precision screening for familial hypercholesterolaemia: a machine learning study applied to electronic health encounter data. *Lancet Digit Health.* 2019;1(8):e393–402. https://doi.org/10.1016/s2589-7500(19)30150-5.
64. Ayoub A, Akyea RK, Silva L, et al. Advancing familial hypercholesterolaemia (FH) screening in primary care: an updated systematic review of systematic screening methods for identificaton of FH. *Br J Gen Pract.* 2024;74(suppl 1):bjgp24X738141. https://doi.org/10.3399/bjgp24X738141.
65. Harris WR, Hernandez MS, Ngo KNH, et al. Electronic health records-based algorithms to screen for U.S. Centers for Disease Control and Prevention tier 1 genetic diseases: a scoping review. *J Am Med Inform Assoc.* 2025;32(10):1629–1637. https://doi.org/10.1093/jamia/ocaf140.
66. Pepplinkhuizen S, Ibrahim S, Vink R, et al. Electronic health records to facilitate continuous detection of familial hypercholesterolemia. *Atherosclerosis.* 2020;310:83–87. https://doi.org/10.1016/j.atherosclerosis.2020.07.022.
67. Safarova MS, Liu H, Kullo IJ. Rapid identification of familial hypercholesterolemia from electronic health records: the SEARCH study. *J Clin Lipidol.* 2016;10(5):1230–1239. https://doi.org/10.1016/j.jacl.2016.08.001.
68. Jackson CL, Keeton JZ, Eason SJ, et al. Identifying familial hypercholesterolemia using a blood donor screening program with more than 1 million volunteer donors. *JAMA Cardiol.* 2019;4(7):685–689. https://doi.org/10.1001/jamacardio.2019.1518.
69. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. *Pediatrics.* 2011;128(suppl 5):S213–256. https://doi.org/10.1542/peds.2009-2107C.
70. Thompson-Paul AM, Kraus EM, Porter RM, et al. Pediatric lipid screening prevalence using nationwide electronic medical records. *JAMA Netw Open.* 2024;7(7):e2421724. https://doi.org/10.1001/jamanetworkopen.2024.21724.
71. Schubert T, Gidding SS, Jones LK. Overcoming the real and imagined barriers to cholesterol screening in pediatrics. *J Clin Lipidol.* 2024;18(3):e297–307. https://doi.org/10.1016/j.jacl.2024.02.008.
72. de Ferranti SD, Rodday AM, Parsons SK, et al. Cholesterol screening and treatment practices and preferences: a survey of United States Pediatricians. *J Pediatr.* 2017;185:99–105.e102. https://doi.org/10.1016/j.jpeds.2016.12.078.
73. Peterson AL, Bang M, Block RC, et al. Cascade screening and treatment initiation in young adults with heterozygous familial hypercholesterolemia. *J Clin Med.* 2021;10(14):3090. https://doi.org/10.3390/jcm10143090.
74. Goren A, Santos HC, Davis TW, et al. Comparison of clinical decision support tools to improve pediatric lipid screening. *J Pediatr.* 2024;269:113973. https://doi.org/10.1016/j.jpeds.2024.113973.
75. Knowles JW, Rader DJ, Khoury MJ. Cascade screening for familial hypercholesterolemia and the use of genetic testing. *JAMA.* 2017;318(4):381–382. https://doi.org/10.1001/jama.2017.8543.
76. Jackson CL, Huschka T, Borah B, et al. Cost-effectiveness of cascade genetic testing for familial hypercholesterolemia in the United States: a simulation analysis. *Am J Prev Cardiol.* 2021;8:100245. https://doi.org/10.1016/j.ajpc.2021.100245.
77. Defesche JC, Lansberg PJ, Umans-Eckenhausen MA, Kastelein JJ. Advanced method for the identification of patients with inherited hypercholesterolemia. *Semin Vasc Med.* 2004;4(1):59–65. https://doi.org/10.1055/s-2004-822987.
78. Nordestgaard BG, Chapman MJ, Humphries SE, et al. 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.* 2013;34(45):3478-3490a. https://doi.org/10.1093/eurheartj/eht273.
79. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation.* 2019;139(25):e1082–1143. https://doi.org/10.1161/cir.0000000000000625.
80. Roberts MC, Dotson WD, DeVore CS, et al. Delivery of cascade screening for hereditary conditions: a scoping review of the literature. *Health Aff.* 2018;37(5):801–808. https://doi.org/10.1377/hlthaff.2017.1630.
81. Ajufo E, deGoma EM, Raper A, et al. A randomized controlled trial of genetic testing and cascade screening in familial hypercholesterolemia. *Genet Med.* 2021;23(9):1697–1704. https://doi.org/10.1038/s41436-021-01192-z.
82. Campbell-Salome G, Jones LK, Masnick MF, et al. Developing and optimizing innovative tools to address familial hypercholesterolemia underdiagnosis: identification methods, patient activation, and cascade testing for familial hypercholesterolemia. *Circ Genom Precis Med.* 2021;14(1):e003120. https://doi.org/10.1161/circgen.120.003120.
83. Miller AA, Bangash H, Smith CY, Wood-Wentz CM, Bailey KR, Kullo IJ. A pragmatic clinical trial of cascade testing for familial hypercholesterolemia. *Genet Med.* 2022;24(12):2535–2543. https://doi.org/10.1016/j.gim.2022.08.026.
84. Umans-Eckenhausen MA, Defesche JC, Sijbrands EJ, et al. Review of first 5 years of screening for familial hypercholesterolaemia in the Netherlands. *Lancet.* 2001;357(9251):165–168. https://doi.org/10.1016/s0140-6736(00)03587-xF.
85. Newson AJ, Humphries SE. Cascade testing in familial hypercholesterolaemia: how should family members be contacted? *Eur J Hum Genet.* 2005;13(4):401–408. https://doi.org/10.1038/sj.ejhg.5201360.
86. Safarova MS, Kullo IJ. Lessening the burden of familial hypercholesterolemia using health information technology. *Circ Res.* 2018;122(1):26–27. https://doi.org/10.1161/circresaha.117.312319.
87. Henrikson NB, Wagner JK, Hampel H, et al. What guidance does HIPAA offer to providers considering familial risk notification and cascade genetic testing? *J Law Biosci.* 2020;7(1):lsaa071. https://doi.org/10.1093/jlb/lsaa071.
88. Schwiter R, Brown E, Murray B, et al. Perspectives from individuals with familial hypercholesterolemia on direct contact in cascade screening. *J Genet Couns.* 2020;29(6):1142–1150. https://doi.org/10.1002/jgc4.1266.
89. McGowan MP, Cuchel M, Ahmed CD, et al. A proof-of-concept study of cascade screening for familial hypercholesterolemia in the US, adapted from the Dutch model. *Am J Prev Cardiol.* 2021;6:100170. https://doi.org/10.1016/j.ajpc.2021.100170.
90. Lee C, Rivera-Valerio M, Bangash H, et al. New case detection by cascade testing in familial hypercholesterolemia: a systematic review

of the literature. *Circ Genom Precis Med.* 2019;12(11):e002723. https://doi.org/10.1161/circgen.119.002723.

91. Lloyd-Jones DM, Braun LT, Ndumele CE, et al. Use of risk assessment tools to guide decision-making in the primary prevention of atherosclerotic cardiovascular disease: a special report from the American Heart Association and American College of Cardiology. *Circulation.* 2019;139(25):e1162–1177. https://doi.org/10.1161/CIR.0000000000000638.
92. Zhou H, Zhang Y, Zhou MM, et al. Evaluation and comparison of the PREVENT and pooled cohort equations for 10-year atherosclerotic cardiovascular risk prediction. *J Am Heart Assoc.* 2025;14(4):e039454. https://doi.org/10.1161/JAHA.124.039454.
93. McKay AJ, Gunn LH, Ray KK. Assessing the external validity of the SAFEHEART risk prediction model in patients with familial hypercholesterolaemia in an English routine care cohort. *Atherosclerosis.* 2022;358:68–74. https://doi.org/10.1016/j.atherosclerosis.2022.07.011.
94. Mata P, Alonso R, Pérez de Isla L. Atherosclerotic cardiovascular disease risk assessment in familial hypercholesterolemia: does one size fit all? *Curr Opin Lipidol.* 2018;29(6):445–452. https://doi.org/10.1097/MOL.0000000000000553.
95. Catapano F, Galea N, Pambianchi G, et al. Effectiveness of clinical scores in predicting coronary artery disease in familial hypercholesterolemia: a coronary computed tomography angiography study. *Radiol Med.* 2023;128(4):445–455. https://doi.org/10.1007/s11547-023-01610-z.
96. Paquette M, Cariou B, Bernard S, et al. Increased FH-risk-score and diabetes are cardiovascular risk equivalents in heterozygous familial hypercholesterolemia. *Arterioscler Thromb Vasc Biol.* 2024;44(2):505–512. https://doi.org/10.1161/ATVBAHA.123.319957.
97. Gallo A, Charriere S, Vimont A, et al. SAFEHEART risk-equation and cholesterol-year-score are powerful predictors of cardiovascular events in French patients with familial hypercholesterolemia. *Atherosclerosis.* 2020;306:41–49. https://doi.org/10.1016/j.atherosclerosis.2020.06.011.
98. Tamehri Zadeh SS, Chan DC, Pang J, Watts GF. Canadian and French risk scores are valid in identifying cardiovascular disease in Australian patients with familial hypercholesterolemia. *Can J Cardiol.* 2025;41(11):2244–2251. https://doi.org/10.1016/j.cjca.2025.07.042.
99. Paquette M, Bernard S, Cariou B, et al. Familial hypercholesterolemia-risk-score: a new score predicting cardiovascular events and cardiovascular mortality in familial hypercholesterolemia. *Arterioscler Thromb Vasc Biol.* 2021;41(10):2632–2640. https://doi.org/10.1161/ATVBAHA.121.316106.
100. Pérez de Isla L, Alonso R, Mata N, et al. Predicting cardiovascular events in familial hypercholesterolemia: the SAFEHEART Registry (Spanish Familial Hypercholesterolemia Cohort Study). *Circulation.* 2017;135(22):2133–2144. https://doi.org/10.1161/CIRCULATIONAHA.116.024541.
101. Mszar R, Grandhi GR, Valero-Elizondo J, et al. Absence of coronary artery calcification in middle-aged familial hypercholesterolemia patients without atherosclerotic cardiovascular disease. *JACC Cardiovasc Imaging.* 2020;13(4):1090–1092. https://doi.org/10.1016/j.jcmg.2019.11.001.
102. Drouin-Chartier JP, Tremblay AJ, Godbout D, et al. Correlates of coronary artery calcification prevalence and severity in patients with heterozygous familial hypercholesterolemia. *CJC Open.* 2021;3(1):62–70. https://doi.org/10.1016/j.cjco.2020.09.010.
103. Tada H, Kojima N, Yamagami K, et al. Coronary artery calcium among patients with heterozygous familial hypercholesterolaemia. *Eur Heart J Open.* 2023;3(3):oead046. https://doi.org/10.1093/ehjopen/oead046.
104. Gallo A, Pérez de Isla L, Charrière S, et al. The added value of coronary calcium score in predicting cardiovascular events in familial hypercholesterolemia. *JACC Cardiovasc Imaging.* 2021;14(12):2414–2424. https://doi.org/10.1016/j.jcmg.2021.06.011.
105. Miname MH, Bittencourt MS, Moraes SR, et al. Coronary artery calcium and cardiovascular events in patients with familial hypercholesterolemia receiving standard lipid-lowering therapy. *JACC Cardiovasc Imaging.* 2019;12(9):1797–1804. https://doi.org/10.1016/j.jcmg.2018.09.019.
106. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2022 ACC Expert Consensus Decision Pathway on the role of nonstatin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol.* 2022;80(14):1366–1418. https://doi.org/10.1016/j.jacc.2022.07.006.
107. Lee SE, Chang HJ, Sung JM, et al. Effects of statins on coronary atherosclerotic plaques: the PARADIGM study. *JACC Cardiovasc Imaging.* 2018;11(10):1475–1484. https://doi.org/10.1016/j.jcmg.2018.04.015.
108. Kalra DK, Heo R, Valenti V, et al. Role of computed tomography for diagnosis and risk stratification of patients with suspected or known coronary artery disease. *Arterioscler Thromb Vasc Biol.* 2014;34(6):1144–1154. https://doi.org/10.1161/atvbaha.113.302074.
109. Neefjes LA, Ten Kate GJ, Rossi A, et al. CT coronary plaque burden in asymptomatic patients with familial hypercholesterolaemia. *Heart.* 2011;97(14):1151–1157. https://doi.org/10.1136/hrt.2010.220699.
110. Miname MH, Ribeiro MS, Parga Filho J, et al. Evaluation of subclinical atherosclerosis by computed tomography coronary angiography and its association with risk factors in familial hypercholesterolemia. *Atherosclerosis.* 2010;213(2):486–491. https://doi.org/10.1016/j.atherosclerosis.2010.10.001.
111. Tada H, Kawashiri MA, Okada H, et al. Assessment of coronary atherosclerosis in patients with familial hypercholesterolemia by coronary computed tomography angiography. *Am J Cardiol.* 2015;115(6):724–729. https://doi.org/10.1016/j.amjcard.2014.12.034.
112. Neefjes LA, Ten Kate GJ, Alexia R, et al. Accelerated subclinical coronary atherosclerosis in patients with familial hypercholesterolemia. *Atherosclerosis.* 2011;219(2):721–727. https://doi.org/10.1016/j.atherosclerosis.2011.09.052.
113. Pérez de Isla L, Díaz-Díaz JL, Romero MJ, et al. Alirocumab and coronary atherosclerosis in asymptomatic patients with familial hypercholesterolemia: the ARCHITECT study. *Circulation.* 2023;147(19):1436–1443. https://doi.org/10.1161/circulationaha.122.062557.
114. Pérez de Isla L, Alonso R, Muñiz-Grijalvo O, et al. Coronary computed tomographic angiography findings and their therapeutic implications in asymptomatic patients with familial hypercholesterolemia. Lessons from the SAFEHEART study. *J Clin Lipidol.* 2018;12(4):948–957. https://doi.org/10.1016/j.jacl.2018.04.003.
115. Reeskamp LF, Nurmohamed NS, Bom MJ, et al. Marked plaque regression in homozygous familial hypercholesterolemia. *Atherosclerosis.* 2021;327:13–17. https://doi.org/10.1016/j.atherosclerosis.2021.04.014.
116. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med.* 2017;376(18):1713–1722. https://doi.org/10.1056/NEJMoa1615664.
117. Bohula EA, Marston NA, Bhatia AK, et al. Evolocumab in patients without a previous myocardial infarction or stroke. *N Engl J Med.* 2026;394(2):117–127. https://doi.org/10.1056/NEJMoa2514428.
118. Luirink IK, Wiegman A, Kusters DM, et al. 20-Year follow-up of statins in children with familial hypercholesterolemia. *N Engl J Med.* 2019;381(16):1547–1556. https://doi.org/10.1056/NEJMoa1816454.
119. Guirguis-Blake JM, Evans CV, Coppola EL, et al. Screening for lipid disorders in children and adolescents: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA.* 2023;330(3):261–274. https://doi.org/10.1001/jama.2023.8867.
120. Mach F, Koskinas KC, Roeters van Lennep JE, et al. 2025 Focused update of the 2019 ESC/EAS Guidelines for the management of

dyslipidaemias. *Eur Heart J.* 2025;46(42):4359–4378. https://doi.org/10.1093/eurheartj/ehaf190.

121. Puri R, Bansal M, Mehta V, et al. Lipid Association of India 2023 update on cardiovascular risk assessment and lipid management in Indian patients: consensus statement IV. *J Clin Lipidol.* 2024;18(3):e351–373. https://doi.org/10.1016/j.jacl.2024.01.006.
122. Giugliano RP, Pedersen TR, Park JG, et al. Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial. *Lancet.* 2017;390(10106):1962–1971. https://doi.org/10.1016/S0140-6736(17)32290-0.
123. Ray KK, Ginsberg HN, Davidson MH, et al. Reductions in atherogenic lipids and major cardiovascular events: a pooled analysis of 10 ODYSSEY trials comparing alirocumab with control. *Circulation.* 2016;134(24):1931–1943. https://doi.org/10.1161/CIRCULATIONAHA.116.024604.
124. Duell PB, Gidding SS, Andersen RL, et al. Longitudinal low density lipoprotein cholesterol goal achievement and cardiovascular outcomes among adult patients with familial hypercholesterolemia: the CASCADE FH registry. *Atherosclerosis.* 2019;289:85–93. https://doi.org/10.1016/j.atherosclerosis.2019.08.007.
125. de Ferranti SD, Steinberger J, Ameduri R, et al. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association. *Circulation.* 2019;139(13):e603–634. https://doi.org/10.1161/CIR.0000000000000618.
126. Williams L, Baker-Smith CM, Bolick J, et al. Nutrition interventions for youth with dyslipidemia: a National Lipid Association clinical perspective. *J Clin Lipidol.* 2022;16(6):776–796. https://doi.org/10.1016/j.jacl.2022.07.011.
127. Kirkpatrick CF, Sikand G, Petersen KS, et al. Nutrition interventions for adults with dyslipidemia: a clinical perspective from the National Lipid Association. *J Clin Lipidol.* 2023;17(4):428–451. https://doi.org/10.1016/j.jacl.2023.05.099.
128. Shams-White MM, Pannucci TE, Lerman JL, et al. Healthy Eating Index-2020: review and update process to reflect the dietary guidelines for Americans, 2020-2025. *J Acad Nutr Diet.* 2023;123(9):1280–1288. https://doi.org/10.1016/j.jand.2023.05.015.
129. Dietary Guidelines for Americans, 2020–2025. 9th ed.; Services, U. S. D. o. A. a. U. S. D. o. H. a. H., Ed.; 2020. https://www.dietaryguidelines.gov/sites/default/files/2020-12/DGA_2020-2025_ExecutiveSummary_English.pdf. Accessed Feb 13, 2026.
130. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the primary prevention of cardiovascular disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation.* 2019;140(11):e563–595. https://doi.org/10.1161/CIR.0000000000000677.
131. Piercy KL, Troiano RP, Ballard RM, et al. The physical activity guidelines for Americans. *JAMA.* 2018;320(19):2020–2028. https://doi.org/10.1001/jama.2018.14854.
132. Vannice G, Rasmussen H. Position of the academy of nutrition and dietetics: dietary fatty acids for healthy adults. *J Acad Nutr Diet.* 2014;114(1):136–153. https://doi.org/10.1016/j.jand.2013.11.001.
133. Lichtenstein AH, Appel LJ, Vadiveloo M, et al. 2021 Dietary guidance to improve cardiovascular health: a scientific statement from the American Heart Association. *Circulation.* 2021;144(23):e472–487. https://doi.org/10.1161/CIR.0000000000001031.
134. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J.* 2021;42(34):3227–3337. https://doi.org/10.1093/eurheartj/ehab484.
135. Banach M, Catapano AL, Cicero AFG, et al. Red yeast rice for dyslipidaemias and cardiovascular risk reduction: a position paper of the International Lipid Expert Panel. *Pharmacol Res.* 2022;183:106370. https://doi.org/10.1016/j.phrs.2022.106370.
136. Cheeley MK, Saseen JJ, Agarwala A, et al. NLA scientific statement on statin intolerance: a new definition and key considerations for ASCVD risk reduction in the statin intolerant patient. *J Clin Lipidol.* 2022;16(4):361–375. https://doi.org/10.1016/j.jacl.2022.05.068.
137. Warden BA, Guyton JR, Kovacs AC, et al. Assessment and management of statin-associated muscle symptoms (SAMS): a clinical perspective from the National Lipid Association. *J Clin Lipidol.* 2023;17(1):19–39. https://doi.org/10.1016/j.jacl.2022.09.001.
138. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med.* 2015;372(25):2387–2397. https://doi.org/10.1056/NEJMoa1410489.
139. Ballantyne CM, Gellis L, Tardif JC, et al. Efficacy and safety of oral PCSK9 inhibitor enlicitide in adults with heterozygous familial hypercholesterolemia: a randomized clinical trial. *JAMA.* 2026;335(2):129–139. https://doi.org/10.1001/jama.2025.20620.
140. Bittner VA, Szarek M, Aylward PE, et al. Effect of alirocumab on lipoprotein(a) and cardiovascular risk after acute coronary syndrome. *J Am Coll Cardiol.* 2020;75(2):133–144. https://doi.org/10.1016/j.jacc.2019.10.057.
141. Marrs JC, Anderson SL. Inclisiran for the treatment of hypercholesterolaemia. *Drugs Context.* 2024;13:2023-12-3. https://doi.org/10.7573/dic.2023-12-3.
142. Lerodalcibep prescribing information. Accessed January 4, 2026. https://www.lerochol.com/.
143. Raal F, Fourie N, Scott R, et al. Long-term efficacy and safety of lerodalcibep in heterozygous familial hypercholesterolaemia: the LIBerate-HeFH trial. *Eur Heart J.* 2023;44(40):4272–4280. https://doi.org/10.1093/eurheartj/ehad596.
144. Raal FJ, Mehta V, Kayikcioglu M, et al. Lerodalcibep and evolocumab for the treatment of homozygous familial hypercholesterolaemia with PCSK9 inhibition (LIBerate-HoFH): a phase 3, randomised, open-label, crossover, non-inferiority trial. *Lancet Diabetes Endocrinol.* 2025;13(3):178–187.
145. Duell PB, Banach M, Catapano AL, et al. Efficacy and safety of bempedoic acid in patients with heterozygous familial hypercholesterolemia: analysis of pooled patient-level data from phase 3 clinical trials. *J Clin Lipidol.* 2024;18(2):e153–165. https://doi.org/10.1016/j.jacl.2023.12.005.
146. Warden BA, Duell PB. Real-world evaluation of bempedoic acid use in patients with homozygous familial hypercholesterolemia. *J Clin Lipidol.* 2026;20(1):96–103. https://doi.org/10.1016/j.jacl.2025.10.065.
147. Nissen SE, Lincoff AM, Brennan D, et al. Bempedoic acid and cardiovascular outcomes in statin-intolerant patients. *N Engl J Med.* 2023;388(15):1353–1364. https://doi.org/10.1056/NEJMoa2215024.
148. Warden BA, Purnell JQ, Duell PB, Fazio S. Real-world utilization of bempedoic acid in an academic preventive cardiology practice. *J Clin Lipidol.* 2022;16(1):94–103. https://doi.org/10.1016/j.jacl.2021.11.013.
149. Walldius G, Erikson U, Olsson AG, et al. The effect of probucol on femoral atherosclerosis: the Probucol Quantitative Regression Swedish Trial (PQRST). *Am J Cardiol.* 1994;74(9):875–883. https://doi.org/10.1016/0002-9149(94)90579-7.
150. Yamashita S, Bujo H, Arai H, et al. Long-term probucol treatment prevents secondary cardiovascular events: a cohort study of patients with heterozygous familial hypercholesterolemia in Japan. *J Atheroscler Thromb.* 2008;15(6):292–303. https://doi.org/10.5551/jat.e610.
151. Yamashita S, Arai H, Bujo H, et al. Probucol Trial for Secondary Prevention of Atherosclerotic Events in Patients with Coronary Heart Disease (PROSPECTIVE). *J Atheroscler Thromb.* 2021;28(2):103–123. https://doi.org/10.5551/jat.55327.
152. Raal F, Durst R, Bi R, et al. Efficacy, safety, and tolerability of inclisiran in patients with homozygous familial hypercholesterolemia: results from the ORION-5 randomized clinical trial. *Circulation.* 2024;149(5):354–362. https://doi.org/10.1161/CIRCULATIONAHA.122.063460.
153. Thedrez A, Blom DJ, Ramin-Mangata S, et al. Homozygous familial hypercholesterolemia patients with identical mutations variably express the LDLR (low-density lipoprotein receptor): implications for the efficacy of evolocumab. *Arterioscler Thromb Vasc Biol.* 2018;38(3):592–598. https://doi.org/10.1161/ATVBAHA.117.310217.
154. Cuchel M, Meagher EA, du Toit Theron H, et al. Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with

homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study. *Lancet.* 2013;381(9860):40–46. https://doi.org/10.1016/S0140-6736(12)61731-0.

155. Blom DJ, Averna MR, Meagher EA, et al. Long-term efficacy and safety of the microsomal triglyceride transfer protein inhibitor lomitapide in patients with homozygous familial hypercholesterolemia. *Circulation.* 2017;136(3):332–335. https://doi.org/10.1161/CIRCULATIONAHA.117.028208.
156. D'Erasmo L, Steward K, Cefalù AB, et al. Efficacy and safety of lomitapide in homozygous familial hypercholesterolaemia: the pan-European retrospective observational study. *Eur J Prev Cardiol.* 2022;29(5):832–841. https://doi.org/10.1093/eurjpc/zwab229.
157. Larrey D, D'Erasmo L, O'Brien S, Arca M. Long-term hepatic safety of lomitapide in homozygous familial hypercholesterolaemia. *Liver Int.* 2023;43(2):413–423. https://doi.org/10.1111/liv.15497.
158. Arca M, D'Erasmo L, Cuchel M, et al. Long-term experience with lomitapide treatment in patients with homozygous familial hypercholesterolemia: over 10 years of efficacy and safety data. *J Clin Lipidol.* 2025;19(4):775–789. https://doi.org/10.1016/j.jacl.2025.03.015.
159. The JUXTAPID® Risk Evaluation and Mitigation Strategy (REMS). Accessed January 4, 2026. https://www.juxtapid.com/rems/.
160. Blom DJ, Gaudet D, Hegele RA, et al. A case series assessing the effects of lomitapide on carotid intima-media thickness in adult patients with homozygous familial hypercholesterolaemia in a real-world setting. *Adv Ther.* 2022;39(4):1857–1870. https://doi.org/10.1007/s12325-021-02031-y.
161. Masana L, Zambon A, Schmitt CP, et al. Lomitapide for the treatment of paediatric patients with homozygous familial hypercholesterolaemia (APH-19): results from the efficacy phase of an open-label, multicentre, phase 3 study. *Lancet Diabetes Endocrinol.* 2024;12(12):880–889. https://doi.org/10.1016/S2213-8587(24)00233-X.
162. Raal FJ, Rosenson RS, Reeskamp LF, et al. Evinacumab for homozygous familial hypercholesterolemia. *N Engl J Med.* 2020;383(8):711–720. https://doi.org/10.1056/NEJMoa2004215.
163. Wilkinson MJ, Bijlani P, Davidson MH, et al. Real-world effectiveness and safety of evinacumab in children and adults with homozygous familial hypercholesterolemia: a multisite US perspective-brief report. *Arterioscler Thromb Vasc Biol.* 2025;45(7):1310–1315. https://doi.org/10.1161/ATVBAHA.124.322364.
164. Wiegman A, Greber-Platzer S, Ali S, et al. Evinacumab for pediatric patients with homozygous familial hypercholesterolemia. *Circulation.* 2024;149(5):343–353. https://doi.org/10.1161/CIRCULATIONAHA.123.065529.
165. Raal FJ, Rosenson RS, Reeskamp LF, et al. The long-term efficacy and safety of evinacumab in patients with homozygous familial hypercholesterolemia. *JACC Adv.* 2023;2(9):100648. https://doi.org/10.1016/j.jacadv.2023.100648.
166. Fornari E, Stefanutti C, Mancioppi V, et al. Safety and effectiveness of evinacumab in an infant with homozygous familial hypercholesterolemia: a new renaissance for the very young? *J Clin Lipidol.* 2025;19(3):689–694. https://doi.org/10.1016/j.jacl.2025.02.012.
167. Stirnkorb C, Ney V, Bergmann C, Bald M. Evinacumab as an adjunct to lipid apheresis in an infant with homozygous familial hypercholesterolemia. *J Pediatr Endocrinol Metab.* 2025;38(4):410–414. https://doi.org/10.1515/jpem-2024-0505.
168. European Commission (EC) extends the approval of Evkeeza® (evinacumab) to children as young as 6-months old with homozygous familial hypercholesterolemia (HoFH). BioSpace; 2025. https://www.biospace.com/press-releases/european-commission-ec-extends-the-approval-of-evkeeza-evinacumab-to-children-as-young-as-6-months-old-with-homozygous-familial-hypercholesterolemia-hofh. Accessed Feb 13, 2026.
169. Regeneron Pharmaceuticals. Evkeeza® (evinacumab-dgnb) ANGPTL3 antibody approved in the U.S. for children as young as 1 year old with ultra-rare form of high cholesterol; September 2025. Accessed January 6, 2026. https://www.evkeeza.com/s/.
170. Béliard S, Saheb S, Litzler-Renault S, et al. Evinacumab and cardiovascular outcome in patients with homozygous familial hypercholesterolemia. *Arterioscler Thromb Vasc Biol.* 2024;44(6):1447–1454. https://doi.org/10.1161/ATVBAHA.123.320609.
171. Vishwanath R, Hemphill LC. Familial hypercholesterolemia and estimation of US patients eligible for low-density lipoprotein apheresis after maximally tolerated lipid-lowering therapy. *J Clin Lipidol.* 2014;8(1):18–28. https://doi.org/10.1016/j.jacl.2013.11.002.
172. Gianos E, Duell PB, Toth PP, et al. Lipoprotein apheresis: utility, outcomes, and implementation in clinical practice: a scientific statement from the American Heart Association. *Arterioscler Thromb Vasc Biol.* 2024;44(12):e304–321. https://doi.org/10.1161/ATV.0000000000000177.
173. Ibrahim M, El-Hamamsy I, Barbir M, Yacoub MH. Translational lessons from a case of combined heart and liver transplantation for familial hypercholesterolemia 20 years post-operatively. *J Cardiovasc Transl Res.* 2012;5(3):351–358. https://doi.org/10.1007/s12265-011-9311-1.
174. Ishigaki Y, Kawagishi N, Hasegawa Y, et al. Liver transplantation for homozygous familial hypercholesterolemia. *J Atheroscler Thromb.* 2019;26(2):121–127. https://doi.org/10.5551/jat.RV17029.
175. Lin D, Lu Y, Qiu B, et al. The therapeutic effect of liver transplantation in 14 children with homozygous familial hypercholesterolemia: a prospective cohort: Liver transplant for familial hypercholesterolemia. *J Clin Lipidol.* 2024;18(6):e1055–1066. https://doi.org/10.1016/j.jacl.2024.08.008.
176. Al-Ashwal A, Al-Mansour S, Al-Shagrani M, et al. The effectiveness of liver transplantation in reducing lipid levels in Saudi children with homozygous familial hypercholesterolemia. *Front Cardiovasc Med.* 2024;11:1454638. https://doi.org/10.3389/fcvm.2024.1454638.
177. Martinez M, Brodlie S, Griesemer A, et al. Effects of liver transplantation on lipids and cardiovascular disease in children with homozygous familial hypercholesterolemia. *Am J Cardiol.* 2016;118(4):504–510. https://doi.org/10.1016/j.amjcard.2016.05.042.
178. Barbir M, Khaghani A, Kehely A, et al. Normal levels of lipoproteins including lipoprotein(a) after liver-heart transplantation in a patient with homozygous familial hypercholesterolaemia. *Q J Med.* 1992;85(307-308):807–812.
179. Elisofon SA, Magee JC, Ng VL, et al. Society of pediatric liver transplantation: current registry status 2011-2018. *Pediatr Transplant.* 2020;24(1):e13605. https://doi.org/10.1111/petr.13605.
180. de Ville de Goyet J, Baumann U, Karam V, et al. European Liver Transplant Registry: donor and transplant surgery aspects of 16,641 liver transplantations in children. *Hepatology.* 2022;75(3):634–645. https://doi.org/10.1002/hep.32223.
181. Cephus CE, Qureshi AM, Sexson Tejtel SK, et al. Coronary artery disease in a child with homozygous familial hypercholesterolemia: regression after liver transplantation. *J Clin Lipidol.* 2019;13(6):880–886. https://doi.org/10.1016/j.jacl.2019.09.007.
182. Mlinaric M, Bratanic N, Dragos V, et al. Case report: liver transplantation in homozygous familial hypercholesterolemia (HoFH)-long-term follow-up of a patient and literature review. *Front Pediatr.* 2020;8:567895. https://doi.org/10.3389/fped.2020.567895.
183. Lefort B, Saheb S, Bruckert E, et al. Impact of LDL apheresis on aortic root atheroma in children with homozygous familial hypercholesterolemia. *Atherosclerosis.* 2015;239(1):158–162. https://doi.org/10.1016/j.atherosclerosis.2015.01.007.
184. Greco M, Robinson JD, Eltayeb O, Benuck I. Progressive aortic stenosis in homozygous familial hypercholesterolemia after liver transplant. *Pediatrics.* 2016;138(5):e20160740. https://doi.org/10.1542/peds.2016-0740.
185. Koschinsky ML, Bajaj A, Boffa MB, et al. A focused update to the 2019 NLA scientific statement on use of lipoprotein(a) in clinical practice. *J Clin Lipidol.* 2024;18(3):e308–319. https://doi.org/10.1016/j.jacl.2024.03.001.
186. Klevmoen M, Bogsrud MP, Retterstøl K, et al. Loss of statin treatment years during pregnancy and breastfeeding periods in women

with familial hypercholesterolemia. *Atherosclerosis.* 2021;335:8–15. https://doi.org/10.1016/j.atherosclerosis.2021.09.003.

187. Agarwala A, Dixon DL, Gianos E, et al. Dyslipidemia management in women of reproductive potential: an Expert Clinical Consensus from the National Lipid Association. *J Clin Lipidol.* 2024;18(5):e664–684. https://doi.org/10.1016/j.jacl.2024.05.005.
188. Karalis G, Hill AN, Clifton S, Wild RA. The risks of statin use in pregnancy: a systematic review. *J Clin Lipidol.* 2016;10(5):1081–1090. https://doi.org/10.1016/j.jacl.2016.07.002.
189. U.S. Food & Drug Administration. FDA requests removal of strongest warning against using cholesterol-lowering statins during pregnancy; still advises most pregnant patients should stop taking statins; 2021.
190. Costantine MM, Cleary K, Hebert MF, et al. Safety and pharmacokinetics of pravastatin used for the prevention of preeclampsia in high-risk pregnant women: a pilot randomized controlled trial. *Am J Obstet Gynecol.* 2016;214(6):720.e1–720.e17. https://doi.org/10.1016/j.ajog.2015.12.038.
191. Costantine MM, West H, Wisner KL, et al. A randomized pilot clinical trial of pravastatin versus placebo in pregnant patients at high risk of preeclampsia. *Am J Obstet Gynecol.* 2021;225(6):666.e1–-666.e15. https://doi.org/10.1016/j.ajog.2021.05.018.
192. Mészáros B, Veres DS, Nagyistók L, et al. Pravastatin in preeclampsia: a meta-analysis and systematic review. *Front Med.* 2022;9:1076372. https://doi.org/10.3389/fmed.2022.1076372.
193. Döbert M, Varouxaki AN, Mu AC, et al. Pravastatin versus placebo in pregnancies at high risk of term preeclampsia. *Circulation.* 2021;144(9):670–679. https://doi.org/10.1161/circulationaha.121.053963.
194. Blaha M, Lanska M, Blaha V, et al. Pregnancy in homozygous familial hypercholesterolemia—importance of LDL-apheresis. *Atheroscler Suppl.* 2015;18:134–139. https://doi.org/10.1016/j.atherosclerosissup.2015.02.024.
195. Wang A, Richhariya A, Gandra SR, et al. Systematic review of low-density lipoprotein cholesterol apheresis for the treatment of familial hypercholesterolemia. *J Am Heart Assoc.* 2016;5(7):e003294. https://doi.org/10.1161/jaha.116.003294.
196. Herrera E, Amusquivar E, López-Soldado I, Ortega H. Maternal lipid metabolism and placental lipid transfer. *Horm Res.* 2006;65(suppl 3):59–64. https://doi.org/10.1159/000091507.
197. Amundsen AL, Khoury J, Iversen PO, et al. Marked changes in plasma lipids and lipoproteins during pregnancy in women with familial hypercholesterolemia. *Atherosclerosis.* 2006;189(2):451–457. https://doi.org/10.1016/j.atherosclerosis.2006.01.002.
198. Amrock SM, Duell PB, Knickelbine T, et al. Health disparities among adult patients with a phenotypic diagnosis of familial hypercholesterolemia in the CASCADE-FH™ patient registry. *Atherosclerosis.* 2017;267:19–26. https://doi.org/10.1016/j.atherosclerosis.2017.10.006.
199. Agarwala A, Deych E, Jones LK, et al. Sex-related differences in premature cardiovascular disease in familial hypercholesterolemia. *J Clin Lipidol.* 2023;17(1):150–156. https://doi.org/10.1016/j.jacl.2022.11.009.
200. Zamora A, Ramos R, Comas-Cufi M, et al. Women with familial hypercholesterolemia phenotype are undertreated and poorly controlled compared to men. *Sci Rep.* 2023;13(1):1492. https://doi.org/10.1038/s41598-023-27963-z.
201. Agarwala A, Bekele N, Deych E, et al. Racial disparities in modifiable risk factors and statin usage in black patients with familial hypercholesterolemia. *J Am Heart Assoc.* 2021;10(17):e020890. https://doi.org/10.1161/jaha.121.020890.
202. McGowan MP, Xing C, Khera A, et al. Using healthcare claims data to identify health disparities for individuals with familial hypercholesterolemia. *J Clin Lipidol.* 2025;19(4):1020–1028. https://doi.org/10.1016/j.jacl.2025.04.199.
203. Wilemon KA, Patel J, Aguilar-Salinas C, et al. Reducing the clinical and public health burden of familial hypercholesterolemia: a global call to action. *JAMA Cardiol.* 2020;5(2):217–229. https://doi.org/10.1001/jamacardio.2019.5173.
204. Krol M, Brouwer W. How to estimate productivity costs in economic evaluations. *Pharmacoeconomics.* 2014;32(4):335–344. https://doi.org/10.1007/s40273-014-0132-3.
205. Weintraub WS, Daniels SR, Burke LE, et al. Value of primordial and primary prevention for cardiovascular disease: a policy statement from the American Heart Association. *Circulation.* 2011;124(8):967–990. https://doi.org/10.1161/CIR.0b013e3182285a81.
206. Meng R, Wei Q, Zhou J, et al. A systematic review of cost-effectiveness analysis of different screening strategies for familial hypercholesterolemia. *J Clin Lipidol.* 2024;18(1):e21–32. https://doi.org/10.1016/j.jacl.2023.11.001.