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REVIEW

Familial hypercholesterolemia: state-of-the-art

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Abstract

Familial hypercholesterolemia (FH) affects about 20 million people worldwide and remains markedly underdiagnosed and undertreated. Contemporary studies estimate the prevalence of heterozygous FH (HeFH) at 1 in 192 to 1 in 310, and the prevalence of homozygous FH (HoFH) at about 1 in 300,000. The 2016 United States National Health and Nutrition Examination Survey estimated FH prevalence at 1 in 250 adults. Untreated HeFH causes fatal coronary events before age 55 in about 50% of men and before age 60 in about 15% of women. Pathogenic variants in the low-density lipoprotein receptor, apolipoprotein B, or proprotein convertase subtilisin/kexin type 9 (PCSK9) cause most FH cases. Polygenic burden and genetic modifiers influence phenotype and treatment response. Clinical diagnosis relies on the Dutch Lipid Clinic Network (DLCN), the Simon Broome criteria, or the Make Early Diagnosis to Prevent Early Death criteria. Next-generation sequencing (NGS) increases diagnostic certainty and enables cascade screening. In severe hypercholesterolemia, NGS detects mutations in 57% of cases overall and in 92% when low-density lipoprotein cholesterol (LDL-C) exceeds 310 mg/dL. In contrast, population screening using LDL-C >190 mg/dL identifies pathogenic variants in fewer than 5% of cases. Cascade screening yields range from 0.4 to 0.7 per index case in some United Kingdom series, about 2 in several Australian and Brazilian programs, and up to 8 in optimized Dutch programs. In primary care, the Familial Hypercholesterolemia Case Ascertainment Tool discriminated FH better than other criteria in 1,030,183 patients, with an area under the curve (AUC) of 0.844, compared with 0.730 for Simon Broome, 0.766 for DLCN, and 0.579 for LDL-C above the 99th percentile. Management begins with high-intensity statins and ezetimibe. Treatment aims for at least a 50% reduction in LDL-C and LDL-C <70 mg/dL for primary prevention or <55 mg/dL for very-high-risk patients. In children older than 10 years, the LDL-C target is <135 mg/dL. PCSK9-directed therapies further lower LDL-C. Evolocumab reduces LDL-C by 59% to 61% in RUTHERFORD-2 and by 31% in TESLA Part B; alirocumab reduces LDL-C by 51% to 58% in ODYSSEY FH I/II; inclisiran reduces LDL-C by 48% in ORION-9; and evinacumab reduces LDL-C by about 49% in HoFH. Lipoprotein apheresis acutely reduces LDL-C by about 50% to 75% per session. Earlier detection, cascade screening, and equitable access to combination therapy remain central to reducing premature atherosclerotic cardiovascular disease in FH.

Key words: familial hypercholesterolemia, low-density lipoprotein cholesterol, LDL-C, atherosclerotic cardiovascular disease, ASCVD.

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Introduction

Familial hypercholesterolemia (FH) is an inherited disorder of lipid metabolism characterized by lifelong elevation of low-density lipoprotein cholesterol (LDL-C) and predisposes patients to premature atherosclerotic cardiovascular disease (ASCVD).[1,2] It is one of the most common inherited diseases, affecting about 20 million people globally, but remains largely underdiagnosed and undertreated.[3-6] The 2016 United States (US) National Health and Nutrition Examination Surveys (NHANES) estimated that FH affects approximately 1 in 250 adults in the country, with similar prevalence across sexes but higher prevalence among

those with obesity and Black adults.[7] Earlier estimates suggested that heterozygous FH (HeFH) affects 1 in 500 people and homozygous FH (HoFH) affects 1 in 1,000,000 individuals.[2,8-10] However, contemporary population-based studies show that HeFH is up to two-fold more prevalent, with estimates ranging from nearly 1 in 192 to 1 in 310 across Europe, North America, and Australia.[11-14] Additionally, HoFH prevalence is now estimated at about 1 in 300,000 in contemporary cohorts.[15]

FH produces characteristic physical signs from lifelong LDL-C elevation. Patients commonly develop tendon and cutaneous xanthomas (classically of the Achilles and finger extensor tendons), corneal arcus, and xanthelasma.[8,16] These extravascular lipid deposits accompany accelerated arterial plaque formation and early coronary heart disease (CHD), and drive the excess morbidity and mortality observed in affected families.[8,16] The clinical course also varies with genetic burden. HeFH frequently presents as premature coronary disease in adulthood, whereas HoFH produces markedly higher LDL-C, severe atherosclerosis, and cardiovascular events like myocardial infarction (MI) at much younger ages, thus generally requiring early, aggressive, and multimodal therapy.[17,18] Research further shows that if left untreated, HeFH can carry substantial early mortality, with approximately 50% of affected men and 15% of affected women experiencing fatal coronary events before ages 55 and 60, respectively.[19,20] Nevertheless, early diagnosis and sustained LDL-lowering may significantly reduce the excess cardiovascular risk.[21,22] Additionally, founder effects increase local prevalence in certain populations (*e.g.*, French Canadians, Afrikaners, Ashkenazi Jews, Icelanders, Christian Lebanese, Tunisians, Gujarati South African Indians, and Finns),[2] and consanguinity increases HoFH frequency in affected communities.[23]

Clinicians diagnose FH primarily by clinical assessment, supplemented by standardized scoring systems and genetic testing. The Dutch Lipid Clinic Network (DLCN) score is the most commonly used adult tool; however, it is not validated for the pediatric population.[24,25] The Simon Broome criteria apply to both adults and children and integrate physical signs, lipid levels, family history, and DNA results.[26] Similarly, the Make Early Diagnosis to Prevent Early Death (MEDPED) criteria uses age- and family-specific LDL-C cutoffs, and therefore, requires lipid data of relatives as well.[25,27] While therapeutic advances have transformed prognosis, they have not yet eliminated gaps in care. Statins remain first-line therapy for HeFH and HoFH, and their introduction substantially lowered FH-associated mortality compared with the pre-statin era.[23,28-30] However, only a minority of diagnosed patients receive optimal, guideline-recommended therapy, with estimates ranging from approximately 10-25%, and many affected individuals fail to achieve LDL-C targets without combination or novel therapies.[31]

Despite available diagnostics and effective lipid-lowering agents, many affected individuals with FH remain undetected and undertreated, continuing avoidable morbidity and mortality. Systematic family-based or cascade screening and expanded pediatric case finding offer the most optimal routes to close detection gaps and enable earlier, lifelong prevention.[32] Additionally, national and international registries, guideline initiatives, and implementation programs now prioritize case identification, genetic confirmation when feasible, and swift escalation to combination or novel therapies for patients who do not reach LDL-C targets on statins alone.[33] Important health-system barriers, including variable access to advanced lipid-lowering agents, low uptake of genetic testing, inconsistent cascade implementation, and weak linkage of identified patients into coordinated care pathways limit the practical effect of these advances and warrant targeted implementation research. Accordingly, this state-of-the-art review integrates current evidence on the genetics, screening, diagnosis, and management of familial hypercholesterolemia.

Pathophysiology of familial hypercholesterolemia

The dominant molecular cause of FH is impaired hepatic clearance of LDL-C, resulting from defects in the LDL-receptor pathway. Elevated lipoprotein(a) [Lp(a)] also contributes to ASCVD risk in many patients with FH and acts as an important independent risk modifier. Mutations in the LDLR gene account for the majority of cases (~80-85%) and produce either reduced receptor synthesis, impaired ligand binding, defective trafficking to the plasma membrane, or failure of internalization after LDL binding.[34-36] These defects decrease hepatocyte uptake of LDL particles, consequently elevating circulating LDL-C, and ultimately resulting in endothelial dysfunction, atherosclerosis, and increase risk for strokes.[35-37]

Apolipoprotein B 100 (ApoB-100) mutations are the next most frequent monogenic cause, accounting for 5-10% of cases. They disrupt the apolipoprotein ligand required for LDLR recognition, thereby lowering LDL affinity for the receptor and reducing hepatic clearance.[19,38] Gain-of-function (GOF) variants in the proprotein convertase subtilisin/kexin type 9 (PCSK9) are less common (~2%) but exert outsized effects by accelerating LDLR degradation.[39] Conversely, loss-of-function (LOF) PCSK9 variants reduce LDL-C. Both classes of PCSK9 variants reduce LDLR expression, leading to plasma LDL accumulation.[39] In addition, autosomal-recessive FH results from rare defects in LDLR-adaptor protein (LDLRAP1), which impair receptor-mediated endocytosis in hepatocytes and peripheral cells.[2]

At the tissue level, prolonged LDL-C elevation promotes retention and modification of LDL particles in the arterial intima, macrophage uptake of modified LDL, foam-cell formation, and accelerated atheroma development.[3,19,40] HoFH patients commonly exhibit far higher LDL-C concentrations and earlier, more aggressive atherosclerosis than heterozygotes.[3,19] This reflects biallelic impairment of LDLR function or compound genetic defects. Compound heterozygotes and double heterozygotes, which are pathogenic variants in two different FH genes, produce intermediate or severe phenotypes depending on residual receptor activity.[3,19]

FH is also associated with additional lipoprotein abnormalities that may influence risk. Many patients have elevated Lp(a) con-

centrations, which are often higher in HoFH than HeFH.[41] Interestingly, some HoFH cohorts show reduced high-density lipoprotein (HDL)-mediated cholesterol efflux.[41] Researchers have catalogued over 1200 distinct LDLR variants, and the specific mutation class (null *vs*. defective) strongly predicts on-treatment LDL lowering and response to LDLR-dependent therapies.[3] Moreover, when no monogenic cause is found, a polygenic burden of small-effect LDL-raising alleles or undiscovered rare genes commonly explains a clinical FH phenotype, which justifies the continued use of clinical diagnostic criteria alongside molecular testing.[42]

Genetics of familial hypercholesterolemia

FH results from a range of genetic architectures, predominantly monogenic autosomal-dominant disorders, but also rare autosomal-recessive forms and frequent polygenic contributions. These architectures determine LDL-C magnitude, age at clinical onset, extra-hepatic features, and response to LDLR-dependent *versus* LDLR-independent therapies.[2,43,44] The major and candidate genes associated with FH phenotype are summarized in Table 1.

Autosomal-dominant hypercholesterolemia

Most autosomal dominant hypercholesterolemia (ADH) cases, including HeFH and HoFH, are caused by pathogenic variants in LDLR, APOB, or PCSK9 genes, with rare contributions from APOE and other *loci*.[45]

The LDLR gene remains the predominant *locus* and explains most genetically confirmed cases. It spans 45 kilobases (kb) on chromosome 19p13.2 and contains 18 exons encoding an 860-amino-acid precursor that is processed to an 839-amino-

Table 1. Major and candidate genes associated with familial hypercholesterolemia.

Gene	Protein and principal function	Chromosomal *locus* (exons)	Inheritance	Principal molecular effect	Clinical relevance
			Major genes		
LDLR	LDL receptor - mediates hepatic uptake of apoB-containing lipoproteins	19p13.2 (18 exons)	AD	Reduced LDLR binding/trafficking resulting in impaired LDL clearance	Most common monogenic cause of FH; accounts for ~90-95% of pathogenic monogenic variants
APOB	ApoB-100 - primary LDL ligand for LDLR	2p24.1 (29 exons)	AD	Impaired ApoB–LDLR interaction, resulting in reduced LDL uptake	~5% of monogenic FH; phenotypes are often milder and population-dependent
PCSK9	PCSK9 - regulates LDLR degradation	1p32.3 (13 exons)	AD	GOF increases LDLR degradation, leading to higher LDL-C	~3% of FH-pathogenic monogenic variants; GOF mutations cause FH, LOF alleles are protective
LDLRAP1	LDLRAP1 - required for receptor endocytosis	1p36.11 (15 exons)	AR	Disrupted LDLR internalization, leading to functional LDLR deficiency	Biallelic mutations cause autosomal-recessive hypercholesterolemia (milder); heterozygotes are often phenotypically mild
LIPA	Lysosomal acid lipase alias - hydrolyzes cholesterol esters and triglycerides	10q23.31 (10 exons)	AR	Impaired cholesterol ester hydrolysis; secondary effects on hepatic lipid handling	Causes cholesterol ester storage disease (Wolman disease); some splice defects can mimic FH phenotype
			Candidate genes		
ABCG5 / ABCG8	Sterolin-1/2 - sterol transporters for biliary excretion	2p21 (15/14 exons)	AR	Increased plant sterol absorption and retention	Cause sitosterolemia; responds well to ezetimibe
APOE	Apolipoprotein E - lipoprotein remnant handling	19q13.32 (6 exons)	AD (some alleles)	Allele-specific effects on lipoprotein metabolism	Certain in-frame deletions (*e.g.*, Leu167del) reported with FH-like phenotypes
STAP1	Signal-transducing adaptor protein-1 - signaling adaptor	4q13.2 (10 exons)	AD	Unclear / uncertain functional link to LDL metabolism	Association with FH remains provisional and very rare
PNPLA5	Patatin-like phospholipase domain protein 5 - lipid metabolism in adipocytes	22q13.31	AR	Possible impairment of lipolysis	Rare variants linked with very high LDL-C levels
CYP7A1	Cholesterol 7α-hydroxylase - rate-limiting enzyme in bile acid synthesis	8q12.1	AR	Reduced cholesterol catabolism resulting in impaired elimination	Familial reports of FH-like phenotype with impaired bile acid synthesis

AD, Autosomal dominant; AR, Autosomal recessive; Apo, Apolipoprotein; HMG-CoA, Hydroxy-methyl-glutaryl-coenzyme A; LDL, Low-density lipoprotein; LDLR, Low-density lipoprotein receptor; LDLRAP1, LDL receptor adaptor protein 1; PCSK9, Proprotein convertase subtilisin/kexin 9.

acid, 160-kDa mature glycoprotein after signal-peptide cleavage and glycosylation.[46,47] The receptor mediates receptor-dependent endocytosis of apoB-containing lipoproteins in hepatocytes and extrahepatic cells.[46,48] It encodes the hepatic LDL receptor and harbors over 1000 reported sequence variants, including small nucleotide changes, copy-number variants (CNVs), and deep-intronic splice-altering variants detected by whole genome sequencing (WGS).[46,49,50] These variants fall into functional classes (I-V), which comprise class I (no synthesis), class IIa/IIb (trafficking defects), class III (impaired ligand binding), class IV (defective endocytosis), and class V (defective recycling).[46,51,52] Interestingly, carriers of null or receptor-negative alleles, which stop LDLr function, typically produce the most severe biochemical and clinical phenotypes than those with defective receptor mutations.[53-56] Exon-4 variants also frequently associate with a particularly severe phenotype because they interfere with critical ligand-binding repeats.[46,57]

APOB encodes apoB-100, which is the principal LDL ligand for LDLR. Pathogenic APOB variants, (classically p.Arg3527Gln / R3500Q and a few nearby changes in exon 26) impair apoB-100 binding to LDLR and account for nearly 5-10% of autosomal-dominant FH.[58] APOB mutations typically raise LDL-C by approximately 60 to 70 mg/dl, increase atherosclerotic risk and coronary calcification, and may show incomplete penetrance within families.[59-62] Furthermore, both heterozygotes and rare homozygotes show higher proportions of small, dense LDL particles, which may amplify atherogenicity independent of LDL-C levels.[63]

PCSK9 was discovered by positional cloning in families with familial ADH.[64] It encodes a secreted protein that binds the LDLR's EGF-A domain and directs the receptor to lysosomal degradation, consequently reducing LDLR recycling and surface receptor density.[65] This regulatory role led rapidly to therapeutic targeting. The GOF PCSK9 variants, such as the p.(Ser127Arg), p.(Phe216Leu), and p.(Asp374Tyr), cause ADH by enhancing PCSK9 stability, secretion, or LDLR affinity.[16,66-68] On the contrary, the LOF PCSK9 variants, *e.g.*, p.(Tyr142*), p.(Cys679*), and p.(Arg46Leu), lower LDL-C substantially and associate with marked protection from coronary disease.[69,70] Importantly, although many PCSK9 alleles are described in population databases,[71] relatively few are classified as pathogenic for FH.[16]

A limited number of APOE variants and, occasionally, other *loci* have also been associated with ADH. Documented alleles such as p.(Leu167del) segregate with hypercholesterolemia in pedigrees, but APOE contributes only modestly to the overall molecular pathology of FH, and functional data remain limited for many variants.[16,45,72,73] Moreover, some candidate genes, such as STAP1, were previously proposed but have since been excluded as FH genes following extensive evaluation.[74-77] Ongoing gene discovery continues to identify additional *loci* of uncertain significance, such as on chromosomes 16q22.1 and 8q24.22, underscoring the need for careful functional and segregation analyses.[78-80]

Autosomal-recessive hypercholesterolemia

In addition to ADH, rare cases of FH are inherited in an autosomal recessive manner. Autosomal-recessive hypercholesterolemia (ARH) results from biallelic pathogenic variants in low-density lipoprotein receptor adaptor protein 1 (LDLRAP1), which encodes an adaptor protein essential for clathrin-mediated LDLR endocytosis.[81-84] Patients with ARH exhibit a severe phenotype similar to HoFH, though often with slightly lower LDL-C levels and distinct clinical features.[54,85] Moreover, founder mutations are observed in specific populations, such as Sardinia.[85]

Compound/double heterozygosity and genetic modifiers

Some patients carry multiple FH-related variants, either as compound heterozygotes within the same gene or as double heterozygotes among different genes.[15,86,87] These genetic combinations produce a spectrum of phenotypes, ranging from intermediate LDL-C elevation to HoFH-level severity, depending on variant class and residual receptor activity. Conversely, co-inheritance of LDL-lowering modifier alleles, such as a PCSK9 LOF variant, have been shown to lessen disease severity.[88] The identification of modifier genes, including angiopoietin-like protein 3 (ANGPTL3), cholesterol 25-hydroxylase (CH25H), and insulin induced gene 2 (INSIG2), has provided mechanistic knowledge and directly informed the development of new treatment targets, such as ANGPTL3 inhibition for receptor-deficient states.[16,87,89,90]

Polygenic hypercholesterolemia

Large genome-wide association studies (GWAS) have identified hundreds of lipid-associated *loci*.[91-93] The cumulative burden of common LDL-raising alleles, as measured by polygenic risk scores (PRS), comprises a significant proportion of clinically diagnosed, mutation-negative FH cases.[94] Weighted PRSs, such as 12-marker or reduced 6-marker panels, have been found to be generally higher in mutation-negative FH cohorts, supporting a polygenic basis in many patients.[95] However, the optimal construction, thresholds, and clinical utility of PRS remain unresolved. Current sequencing methods detect causative variants in approximately 60-80% of definite FH cases and 20-30% of possible FH cases, reflecting contributions from both monogenic and polygenic factors, as well as undiscovered rare variants.[16,94,96-98]

Revised framework for the classification of hypercholesterolemia

Recent developments in genomics and clinical medicine have led to a practical four-group reclassification of hypercholesterolemia (Table 2). This approach is based on two criteria: the

presence or absence of a pathogenic or likely pathogenic variant in canonical FH genes (LDLR, APOB, PCSK9), and the presence or absence of severe hypercholesterolemia, typically defined as untreated LDL-C ≥190 mg/dL.[99] The framework categorizes individuals into (1) classical FH, characterized by both a pathogenic variant and severe LDL elevation; (2) severe hypercholesterolemia without an identifiable monogenic variant; (3) a genetic-risk state in which a pathogenic variant is present but LDL-C does not reach the severe threshold; and (4) a large group with neither a pathogenic variant nor severe LDL-C elevation. Classical FH is associated with the highest lifetime risk of ASCVD and clear indications for genetic cascade screening and early, intensive lipid-lowering therapy.[55,100] Individuals with severe hypercholesterolemia but negative genetic testing are more prevalent and may have polygenic inheritance or undiscovered causal variants. These individuals still face substantial cardiovascular risk and require aggressive lipid management and biochemical screening of relatives.[55,100,101] Those with a pathogenic variant but without severe LDL elevation represent a genetically defined risk state with variable penetrance and increased lifetime exposure to atherogenic lipoproteins, supporting periodic lipid monitoring and a lower threshold for preventive treatment.[55,99] Finally, individuals without pathogenic variants and severe LDL elevation, should be managed according to standard population-based cardiovascular risk guidelines rather than FH-specific cascade strategies.[55,99,101]

Screening for familial hypercholesterolemia

FH can be screened using World Health Organization (WHO) standards. However, universal screening is currently neither feasible nor cost-effective. Major bodies therefore recommend structured approaches that prioritize early detection and family-based follow-up and note that routine cardiovascular risk calculators, such as the Systematic COronary Risk Evaluation 2 (SCORE2), are not appropriate for monogenic lipid disorders.[42,102]

Cascade screening (CS), defined as the systematic testing of relatives of a confirmed index case, remains the internationally recommended and most cost-effective strategy for FH detection.[103,104] The highest case identification is achieved when biochemical testing is combined with genetic confirmation of a familial pathogenic variant. Organized national programs report considerable variation in per-index yields, ranging from approximately 0.4 to 0.7 in some UK series, to about 2 in several Australian and Brazilian reports, and up to 8 in optimized Dutch programs.[105-110] The National Institute for Health and Care Excellence (NICE) recommends using genetic testing when the index mutation is known, as targeted genetic testing of relatives provides the highest specificity.[102] In the absence of genotype information, age- and sex-specific LDL-C thresholds should guide family testing, as adult population cutoffs alone may not be able to identify mutation carriers with more modest LDL elevations.[111,112]

Additional strategies include targeted case finding in high-yield clinical groups,[3] such as younger patients with acute coronary syndrome or premature coronary disease, as well as pediatric or reverse-cascade screening (RCS).[113-115] RCS combines universal and cascade screening by measuring infants' total cholesterol levels during their 15-month vaccinations. If levels are elevated, clinicians use DNA analysis to identify mutations and then test the parents and grandparents. This approach is superior because discrimination between FH and non-FH cases based on LDL-C levels is more accurate in childhood, and using it for one generation could detect and register nearly all FH cases.[113-116]

Table 2. Practical four-group classification of hypercholesterolemia.

Characteristics	Classical familial hypercholesterolemia	Severe hypercholesterolemia	Genetic-risk state for hypercholesterolemia	Neither variant nor severe hypercholesterolemia
LDL-C ≥190 mg/dL	Yes	Yes	No	No
Pathogenic FH variant detected	Yes	No (untested or variant not found)	Yes	No
Estimated population prevalence	~1 in 500	~1 in 20	~1 in 500	>90%
Usual mode of inheritance	Autosomal dominant	Often polygenic or mixed	Variable/incomplete penetrance	NA
Typical physical signs (xanthomas, corneal arcus)	May be present (up to ~50%)	Rare or absent	Generally absent	Absent
Principal implicated genes	Heterozygous variants in LDLR, APOB, PCSK9	NA	Heterozygous variants in LDLR, APOB, PCSK9	NA
Relative ASCVD risk (*versus* general population)	Markedly higher, often >20-fold	Substantially higher, >5-fold	Moderately increased, >2-fold	Reference population risk
Is genetic cascade screening recommended	Yes - recommended for relatives	No - routine genetic cascade testing not usually productive	Yes - consider cascade testing and family follow-up	No
Is biochemical (lipid) cascade screening recommended	Yes	Yes	Yes	No

APOB, Apolipoprotein B; ASCVD, Atherosclerotic cardiovascular disease; LDL-C, Low-density lipoprotein cholesterol; LDLR, Low-density lipoprotein receptor; mg/dL, Milligrams per deciliter; mmol/L, Millimoles per liter; PCSK9, Proprotein convertase subtilisin/kexin type 9.

However, local evaluation of cost-effectiveness, logistics, and ethical aspects is necessary before broad implementation could be applied.[117] Moreover, practical screening procedures integrate repeat biochemical measurements, such as total cholesterol and LDL-C (while excluding secondary causes), age-appropriate cutoffs for relatives, and genetic testing using next-generation sequencing (NGS) with copy number variant (CNV) analysis when available.[118] NGS increases diagnostic yield and effectiveness compared to older methods,[119,120] especially when integrated with clinical criteria.[121,122] Thus, high population coverage is achieved in effective programs when testing capacity, clinician education, secure family communication, health system support, and scalable index-case ascertainment with sustained follow-up are integrated.

Diagnosis of familial hypercholesterolemia

FH is diagnosed using clinical and molecular criteria, following the exclusion of secondary causes of hypercholesterolemia such as hypothyroidism, nephrotic syndrome, cholestatic liver disease, significant proteinuria, uncontrolled diabetes, or excessive alcohol intake.[19,123,124] Clinical assessment incorporates personal and family history of premature ASCVD, characteristic physical findings, and repeated LDL-C measurements. Molecular testing is then employed to confirm or refine the diagnosis when available.[123,124]

Clinical diagnostic systems

Several validated clinical algorithms are used to diagnose FH, with the Dutch Lipid Clinic Network (DLCN) score, Simon Broome Register (SBR) criteria, and the MEDPED (Make Early Diagnosis to Prevent Early Death) system being the most widely implemented (Table 3). Despite differences in criteria, these diagnostic systems have similar accuracy, show high specificity but low sensitivity, and there is no consensus on which single system is considered superior over others.[125]

The DLCN score is the most widely used clinical tool for adults.[126] It incorporates LDL-C concentration, family and clinical history, and physical signs such as tendon xanthomas and corneal arcus into a numeric score. This scoring system classifies individuals as having definite, probable, possible, or unlikely FH and assists in triaging patients for genetic testing.[126,127] Guidelines typically

Table 3. Principal diagnostic criteria used for familial hypercholesterolemia case identification.

Criteria	Dutch Lipid Clinic Network	Simon Broome Register	Make Early Diagnosis to Prevent Early Death
Family history - CAD	Premature CAD (aged <55 years in men and <60 years in women) [1 point] Premature CeVD or PVD [1 point]	MI in relatives aged <50 years (2nd-degree*) or <60 years (1st-degree*)	-
Family history - LDL levels, mg/dL (mmol/L)	Relative with LDL-C >95th percentile: - Child [2 points] - Adult [1 point]	LDL-C >290 (7.5) in 1st - or 2nd-degree* relatives	-
Family stigmata	Tendon xanthomas and/or corneal arcus recorded in family [2 points]	Tendon xanthoma in 1st - or 2nd-degree* relatives	-
Personal clinical history	Premature CAD (aged <55 years in men and <60 years in women) [2 points] Premature CeVD or PVD [1 point]	-	-
Physical stigmata (exam)	Tendon xanthoma [6 points] Corneal arcus < 45 years [4 points]	Tendon xanthoma	-
Total cholesterol (mg/dL, mmol/L)	-	Adult: >290 (7.5) Child >260 (6.7)	-
LDL-C (mg/dL, mmol/L)	>325 (>8.5) [8 points] 251-325 (6.5-8.4) [5 points] 191-250 (5.0-6.4) [3 points] 155-190 (4.0-4.9) [1 point]	Adult: >190 (4.9) Child: >155 (4.0)	Age - and family-relative LDL thresholds: >220-360 (5.7-9.3) - depending on degree of relation and age
Genetic analysis	Pathogenic mutation in LDLR, APOB or PCSK9 [8 points]	Pathogenic mutations in LDLR, APOB, or PCSK9	-
Diagnostic classification/rule	Definite: >8 points Probable: 6-8 points Possible: 3-5 points	Definite: Clinical criteria (family + lipid) or DNA mutation Probable: per SBR scoring rules (combination of family history and lipid thresholds)	Diagnosis is made if the adjusted LDL-C cut-off (by age and family relation) is met

*1st-degree relatives include parents, siblings, and children; 2nd-degree relatives include grandparents, aunts, uncles, nieces, and nephews; 3rd-degree relatives include first cousins and siblings of grandparents. APOB, Apolipoprotein B; CAD, Coronary artery disease; CeVD, Cerebrovascular disease; FH, Familial hypercholesterolemia; LDL-C, Low-density lipoprotein cholesterol; LDLR, Low-density lipoprotein receptor; mg/dL, Milligrams per deciliter; MI, Myocardial infarction; mmol/L, Millimoles per liter; PCSK9, Proprotein convertase subtilisin/kexin type 9; PVD, Peripheral vascular disease.

recommend molecular testing when the DLCN score indicates probable or definite FH (*e.g.*, DLCN score >5), as genetic confirmation significantly improves diagnostic certainty and allows for cascade testing.[124]

The Simon Broome Register (SBR) criteria integrates lipid levels, family and clinical history, and objective signs, and considers the presence of a pathogenic DNA variant as definitive evidence of FH.[128] Compared with other scoring systems, it demonstrates high specificity, and a causal mutation is identified in the majority of patients meeting *definite* SBR criteria.[2,98,128,129] Hence, SBR is widely used in UK clinical practice and in research settings where genotyping is available as it recognizes DNA as a definitive diagnostic criterion.

Contrary to DLCN and SBR, the US MEDPED applies age- and family-relative total cholesterol thresholds instead of composite clinical scoring.[130] It provides specific cutoffs for first-, second-, and third-degree relatives, making it suitable for cascade screening when relatives' lipid data are accessible.[130,131] However, its simplicity limits diagnostic breadth, as MEDPED does not explicitly include physical signs or genetic results.

A more recent diagnostic tool, the Familial Hypercholesterolemia Case Ascertainment Tool (FAMCAT), has been developed to improve FH detection in primary care.[132] FAMCAT utilizes ten routinely recorded clinical variables, including sex, age, total or LDL cholesterol, triglycerides, lipid-lowering therapy, family history of FH, MI, raised cholesterol, and the presence of diabetes or chronic kidney disease, which reduces the likelihood of monogenic FH (Table 4). Evidence demonstrates that FAMCAT surpasses existing guidelines, such as the DLCN and SBR, in identifying patients with the highest probability of FH within primary care electronic health records. For example, external validation of FAMCAT in a retrospective cohort of 1,030,183 patients from the UK Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) database found that FAMCAT discriminated FH cases more effectively, achieving an AUC (area under the curve) of 0.844 (95% CI: 0.834 to 0.854) *versus* 0.730 for Simon Broome, 0.766 for DLCN, and 0.579 for cholesterol above the 99th percentile.[133]

In addition to broad clinical algorithms, the American Heart Association (AHA) and the European Atherosclerosis Society (EAS) have proposed a simplified classification system. The AHA guidelines recommend diagnosing HeFH in the absence of genetic testing if a child's LDL-C is at least 160 mg/dL or an adult's LDL-C is at least 190 mg/dL on two separate occasions (Table 5).[134] Diagnosis also requires the presence of a first-degree relative with similar lipid findings, premature coronary artery disease, or an FH-causing mutation. HoFH is diagnosed if LDL-C exceeds 400 mg/dL and one or both parents have FH diagnosed by clinical or genetic criteria.[134] HoFH is considered highly likely when untreated LDL-C exceeds 560 mg/dL, or when LDL-C is above 400 mg/dL in conjunction with aortic valve disease or xanthomas before age 20.[134] The EAS defines HoFH as untreated LDL-C exceeding 500 mg/dL or treated LDL-C of at least 300 mg/dL, combined with cutaneous or tendon xanthomas before age 10, or untreated LDL-C levels consistent with HeFH in both parents.[135] Moreover, population-based genetic screening studies indicate that there is no absolute LDL-C threshold for HoFH diagnosis. Interestingly, while untreated LDL-C above 400 mg/dL is suggestive of HoFH, some individuals with genetically confirmed HoFH may present with lower LDL-C levels.[15,135] The EAS/ESC dyslipidemia recommendations for detection and treatment of HeFH is summarized in Table 6.[21]

Table 4. Predictor variables included in the Familial Hypercholesterolemia Case Ascertainment Tool (FAMCAT) algorithm.

Predictor	Categories / definition used by FAMCAT
Sex	Male; Female
Age (years)	16–24; 25–34; 35–44; 45–54; 55–64; 65–74; 75–84
Highest recorded cholesterol (mmol/L)	Ideal: TC ≤5 or LDL-C ≤3.3 High: TC >5 to ≤6.5 or LDL-C >3.3 to ≤4.1 Very high: TC >6.5 to ≤7.5 or LDL-C >4.1 to ≤4.9 Extremely high: TC >7.5 or LDL-C >4.9
Triglycerides (measured within 1 month of highest cholesterol, mmol/L)	Idea: <1.7 Borderline high: ≥1.7 to <2.3 High: ≥2.3 to <5.6 Very high: ≥5.6 Not recorded
Recent lipid-lowering medication (within 1 month of peak cholesterol)	None; Fibrate / bile-acid sequestrant / niacin; Low-potency statin; Medium-potency statin; High-potency statin
Family history of FH	No; Yes
Family history of myocardial infarction	No; Yes
Family history of raised cholesterol	No; Yes
Diabetes	No; Yes (Type 1 or Type 2)
Chronic kidney disease	No; Yes

LDL-C, Low-density lipoprotein cholesterol; mmol/L, Millimoles per liter; TC, Total cholesterol; FH, Familial hypercholesterolemia.

Genetic testing

Genetic testing provides a definitive diagnosis for FH. Modern molecular platforms, such as deoxyribonucleic acid (DNA) array-based chips and NGS with CNV calling have significantly improved detection capabilities.[136-138] Despite decreasing costs, genetic testing remains inconsistently available and is often not reimbursed across health systems. The diagnostic yield depends on patient selection. For instance, studies report that in clinically selected cohorts with severe hypercholesterolemia, the mutation detection rate was 57% overall and increased to 92% when LDL-C exceeded over 310 mg/dL.[139] In contrast, population-

Table 5. American Heart Association (AHA) diagnostic criteria for familial hypercholesterolemia.

Criteria	AHA diagnostic elements
Family history	Premature CAD in a 1st-degree* relative supports clinical diagnosis.
Affected relatives	Presence of an affected 1st-degree* relative (family clustering) is important for clinical diagnosis.
Physical signs	Tendon xanthomas are a classical physical finding and support diagnosis.
Total cholesterol	AHA includes total cholesterol thresholds for children and adults in diagnostic consideration (aligns with clinical scoring systems).
LDL-C thresholds	Heterozygous FH is suspected when LDL-C >190 mg/dL (4.9 mmol/L) in adults or >160 mg/dL (4.0 mmol/L) in children on two occasions plus family history or a causal mutation.Homozygous FH is considered with LDL-C markedly elevated (e.g., >400 mg/dL) or with very high phenotypes.
Genetic testing	A pathogenic variant in LDLR, APOB or PCSK9 confirms diagnosis when present.
Diagnostic rule	Diagnosis integrates LDL-C thresholds with family history, physical signs, or genetic confirmation.

*1st-degree relatives include parents, siblings, and children. AHA, American Heart Association; APOB, Apolipoprotein B; CAD, Coronary artery disease; FH, Familial hypercholesterolemia; LDL-C, Low-density lipoprotein cholesterol; LDLR, Low-density lipoprotein receptor; mg/dL, Milligrams per deciliter; mmol/L, Millimoles per liter; PCSK9, Proprotein convertase subtilisin/kexin type 9.

Table 6. European Society of Cardiology and European Atherosclerosis Society dyslipidemia recommendations for detection and treatment of heterozygous familial hypercholesterolemia.

	Recommendation	Class, Level
Risk estimation	FH patients with established ASCVD or another major risk factor (e.g., hypertension or obesity) should be regarded as very-high-risk. FH patients without ASCVD or additional risk factors are categorized as high-risk.	I, C
Who to evaluate for FH	Consider FH in adults with CHD (men <55 years, women <60 years), in people with relatives who had premature cardiovascular events or tendon xanthomas, in adults with LDL-C >190 mg/dL (>5 mmol/L), in children with LDL-C >150 mg/dL (>4 mmol/L), and in 1st-dgeree* relatives of known FH cases	I, C
Diagnostic approach	Use established clinical algorithms to diagnose FH and confirm with genetic testing when available	I, C
Family testing	Perform cascade screening of relatives once an index case is identified	I, C
Drug strategies in very-high-risk FH	For FH patients with ASCVD (very high-risk) who fail to reach targets on standard therapy, escalate to combination drug regimens	I, C
PCSK9 inhibitors	Add a PCSK9 monoclonal antibody when very-high-risk FH patients do not meet LDL-C goals despite maximally tolerated statin plus ezetimibe	I, C
LDL-C targets - secondary prevention	Aim for ≥50% LDL-C reduction from baseline and an absolute LDL-C <55 mg/dL (<1.4 mmol/L) in FH patients with ASCVD	I, C
LDL-C targets - primary prevention (very high risk)	Consider ≥50% reduction and LDL-C <55 mg/dL (<1.4 mmol/L) for very-high-risk primary prevention FH patients	IIa, C
LDL-C targets - primary prevention (high risk)	Consider ≥50% reduction and LDL-C <70 mg/dL (<1.8 mmol/L) for FH patients classified as high risk without additional major risk factors	IIa, C
Pediatric recommendations - screening	Screen children from age 5 years (earlier if HoFH is suspected)	I, C
Pediatric recommendations - diagnosis	Consider FH in children with LDL-C >150 mg/dL (>4 mmol/L)	I, C
Pediatric recommendations - therapy	Counsel children on a heart-healthy diet and consider initiating statin therapy between ages 8–10 years when indicated; aim for LDL-C <135 mg/dL (~3.5 mmol/L) in those >10 years	IIa, C

*1st-degree relatives include parents, siblings, and children. ASCVD, Atherosclerotic cardiovascular disease; CHD, Coronary heart disease; FH, Familial hypercholesterolemia; HoFH, Homozygous familial hypercholesterolemia; LDL-C, Low-density lipoprotein cholesterol; mg/dL, Milligrams per deciliter; mmol/L, Millimoles per liter; PCSK9, Proprotein convertase subtilisin/kexin type 9.

based screening using a single LDL-C cutoff (>190 mg/dL) identified pathogenic variants in fewer than 5% of individuals.[140] Despite decreasing costs, genetic testing remains inconsistently available and is often not reimbursed across health systems.[141] Thus, it remains underutilized in clinical practice. For example, only 3.9% of clinically diagnosed FH patients in the US Cascade Screening for Awareness and Detection of FH Registry had undergone genetic testing.[142] Its routine use is debated, as elevated LDL-C generally warrants treatment regardless of genotype.[141,142] However, identification of a pathogenic variant refines prognosis and risk stratification, supports earlier and more intensive lipid-lowering interventions, enhances motivation and adherence, and enables unambiguous and cost-efficient cascade testing of relatives, particularly children.[110,142-145] International and specialty organizations recommend offering genetic testing when available after clinical assessment, and several bodies now advocate for broader molecular diagnosis to guide care.[21,118,146-149]

Differential diagnosis and confirmation

It is essential to distinguish FH from other dyslipidemias, including familial combined hyperlipidemia (FCHL) and polygenic hypercholesterolemia with elevated Lp(a), as these conditions also elevate vascular risk and can closely resemble the clinical presentation of FH. FCHL is characterized by serum cholesterol and/or triglyceride levels above the 90th percentile for age- and sex-matched healthy populations, with at least one first-degree relative exhibiting similar lipid abnormalities.[150] FCHL is the most prevalent inherited lipid disorder and constitutes a significant risk factor for vascular disease, with a prevalence of nearly 10 to 20% among MI survivors. Although FCHL demonstrates autosomal dominant inheritance with low penetrance, the specific causative genes have not been identified. In polygenic hypercholesterolemia, Lp(a) is a circulating lipoprotein consisting of an LDL particle covalently linked to apolipoprotein(a). Genetic variation in the apolipoprotein(a) gene primarily determines serum Lp(a) concentrations, and elevated Lp(a) independently increases vascular disease risk.[151,152] Consequently, patients with polygenic hypercholesterolemia and elevated Lp(a) may be misdiagnosed as having FH.

Management of familial hypercholesterolemia

FH management requires prompt initiation of LDL-lowering therapy, along with consideration of noninvasive imaging to detect subclinical atherosclerosis in asymptomatic individuals.[21] Guidelines like the European Society of Cardiology (ESC) 2019 and 2021, EAS 2019 and 2023, and other major multi-society statements recommend high-intensity statin therapy combined with ezetimibe as first-line treatment for most adults with FH.[21,153,154] PCSK9 inhibitors are reserved for patients at very high risk who do not achieve target levels with maximal statin/ezetimibe therapy or who are statin-intolerant. [21,153-156] If additional LDL reduction is necessary, newer agents such as inclisiran or bempedoic acid may be considered according to the American College of Cardiology (ACC) 2022 guidelines.[157] Moreover, patients with insufficient pharmacologic response may be candidates for specialist-directed lipoprotein apheresis.[157] Recent guideline updates and consensus statements have further refined management principles and expanded therapeutic options for FH. The 2025 ESC/EAS focused update emphasizes early and aggressive LDL-lowering in FH, highlighting that FH-specific targets, rather than general population risk calculators, should guide therapy for mutation-positive individuals.[158] In fact, the updated guidelines now strongly recommend using SCORE2 and SCORE2-OP (Older Persons) algorithms to better estimate the 10-year risk of cardiovascular death and morbidity, especially for individuals up to 89 years old.[159] They also incorporate evidence on novel LDL-lowering agents and offers practical algorithms for combination therapy in very-high-risk patients. LDLR-independent therapies such as evinacumab and lomitapide, as well as early apheresis, are prioritized for receptor-negative or refractory patients. In severe, refractory cases, liver transplantation may also be considered as a curative intervention.[44,135]

The recommend treatment targets for FH patients without prior ASCVD should achieve at least a 50% reduction in LDL and an LDL-C below 70 mg/dL, while those at very high risk (prior ASCVD or equivalent) should aim for at least a 50% reduction and LDL-C below 55 mg/dL.[21,153] Simultaneously, it is critical to detect and treat FH in pediatric patients early. Studies recommend lifestyle interventions and consideration of statin therapy beginning at 6 to 10 years of age, with age-appropriate LDL targets and gradual dose escalation from low starting doses.[21,154-157] The current approach to the management of FH is summarized in Table 7.

Pharmacological therapies

Pharmacological therapy for FH focuses on sustained and intensive lowering of LDL-C to reduce lifelong atherosclerotic risk. Management follows a stepwise strategy beginning with statins and ezetimibe, with escalation to PCSK9-targeted or other non-statin agents when treatment goals are not achieved. Drug selection is individualized based on FH phenotype, residual LDL-receptor activity, and overall cardiovascular risk. Novel and gene-based therapies are emerging, particularly for patients with refractory or homozygous disease, further expanding the therapeutic armamentarium (Figure 1).

Statins

Statins, also known as 3-hydroxy-3methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors, inhibit HMG-CoA reductase, reduce hepatic cholesterol synthesis, and upregulate LDL receptors,

thereby lowering circulating LDL-C and modestly increasing HDL cholesterol (HDL-C) levels.[21,160] High-intensity statins typically reduce LDL-C by approximately 50-60%, while moderate- and low-intensity regimens achieve reductions of about 30-50% and 30%, respectively.[161,162] Thus, statin therapy remains the primary intervention for ASCVD prevention.[163] Substantial observational and trial evidence show that statin therapy in FH is associated with significant reductions in ischemic heart disease and major cardiovascular events like MI or CAD mortality.[42,164] For example, one large FH cohort analysis reported a 76% relative decrease in cardiovascular events with statin use.[165] Statins also primarily increase LDL-receptor expression in the liver and this makes HoFH patients with null mutations often unresponsive to statin therapy. However, several studies demonstrate that these patients still respond to statins through alternative mechanisms, such as reduced very-low-density lipoprotein (VLDL) synthesis.[44,166-169] In addition to its therapeutic advantages, statins also have well-characterized adverse effects, including statin-associated muscle symptoms affecting a minority of patients, rare cases of rhabdomyolysis, small increases in transaminases, and a modest elevation in the risk of new-onset diabetes.[21,170-174] Nevertheless, the overall benefit-risk ratio in FH remains strongly favorable. Pediatric data further supports the safety of statins when initiated at low doses with gradual up-titration in children with confirmed FH, and guidelines recommend considering statin therapy in childhood when indicated.[175-177]

Ezetimibe and statin-ezetimibe combination therapy

Ezetimibe inhibits intestinal cholesterol absorption via Niemann-Pick C1-like 1 (NPC1L1) transporter, reduces hepatic cholesterol delivery, and subsequently increases LDL-receptor expression.[21] This results in approximately an 18% incremental reduction in LDL-C as monotherapy and an additional 20% reduction when combined with statin therapy.[178-180] Randomized outcome data from the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) and subsequent analyses demonstrate that LDL-C lowering with ezetimibe leads to incremental reductions in major adverse cardiovascular events (MACE) when used with statins.[180-182] Prespecified subgroup analyses further confirm significant MACE reductions of 24% for each additional 39 mg/dL decrease in LDL-C.[183] Contrary to statins alone, ezetimibe remains effective in many patients with HoFH because it does not directly act via the expression of the LDL receptors.[160] Moreover, the ezetimibe-statin combination therapy has a favorable safety profile, with no increase in myotoxicity beyond that associated with statins, and serious hepatic injury is very rare.[21,184] Although a cancer signal was observed in the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial, subsequent analyses have not substantiated this finding and additional data is required.[185] Current guidelines recommend adding ezetimibe to maximally tolerated statin therapy when LDL-C targets are not achieved. However, many patients with FH require additional non-statin agents to reach desired targets.[21,153,154,157]

PCSK9 monoclonal antibodies

PCSK9 monoclonal antibodies bind circulating PCSK9, prevent LDL-receptor degradation, and increase receptor recycling, resulting in substantial LDL-C reductions of approximately 60% when administered alone or in combination with statins.[21,186,187] Large randomized trials in FH, including the ODYSSEY-FH trials (ODYSSEY FH I, ODYSSEY FH II, ODYSSEY HIGH FH, and ODYSSEY ALTERNATIVE trial) for alirocumab and

Table 7. Practical, stepwise summary of contemporary diagnosis and management of familial hypercholesterolemia.

Steps	Key actions
When to suspect FH	Adults with premature ASCVD (men <55 years; women <60 years) Individuals with a family history of premature ASCVD Relatives with known hypercholesterolemia or tendon xanthomas Adults with LDL-C >190 mg/dL (>4.9 mmol/L) Children with LDL-C >150 mg/dL (>3.9 mmol/L)
How to confirm FH	Exclude secondary causes of raised lipids Apply an established clinical diagnostic algorithm (e.g., DLCN, SBR, MEDPED) Offer genetic testing when available Evaluate concomitant cardiovascular risk factors Initiate family cascade testing using biochemical screening and targeted genetic testing if a causal variant is found
Treatment goals	Adults without prior ASCVD: aim for ≥50% LDL-C reduction and an LDL-C <70 mg/dL (<1.8 mmol/L) Adults with prior ASCVD or equivalent (very high risk): aim for ≥50% reduction and LDL-C <55 mg/dL (<1.4 mmol/L) Children >10 years: target LDL-C <135 mg/dL (<3.5 mmol/L), with lifestyle and age-appropriate pharmacotherapy
Therapeutic strategy	Initiate comprehensive lifestyle counselling plus high-intensity statin therapy as first-line Add ezetimibe if targets are not met on maximally tolerated statin Escalate to a PCSK9 inhibitor (or other approved non-statin agents) when statin + ezetimibe fails to achieve goals or in statin-intolerant patients Consider specialist therapies (e.g., apheresis, lomitapide, evinacumab) for refractory or homozygous FH

ASCVD, Atherosclerotic cardiovascular disease; DLCN, Dutch Lipid Clinic Network; FH, Familial hypercholesterolemia; LDL-C, Low-density lipoprotein cholesterol; MEDPED, Make Early Diagnosis to Prevent Early Death; PCSK9, Proprotein convertase subtilisin/kexin type 9; SBR, Simon Broome Register.

the RUTHERFORD (Randomized Trial Using HeFH Patients to Evaluate the Efficacy of Repatha) and RUTHERFORD 2 trials for evolocumab, as well as outcome trials on a statin background, consistently demonstrate significant LDL-C lowering, high rates of target achievement, and favorable safety profiles.[188-193] The most common adverse events are injection-site reactions and

Figure 1. Pharmacological therapies.

ASCVD, atherosclerotic cardiovascular disease; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; NPC1L1, niemann-pick C1-like 1; PCSK-9, proprotein convertase subtilisin/Kexin type 9; siRNA, small interfering ribonucleic acid; ATP, adenosine triphosphate; CETP, cholesteryl ester transfer protein; HDL, high-density lipoprotein; ANGPTL3, angiopoietin-like protein 3; LDLR, low-density lipoprotein receptor; VLDL, very-low-density lipoprotein; PPAR-α, peroxisome proliferator-activated receptor alpha; ApoB, apolipoprotein B; Lp (a), lipoprotein (a); MTP, microsomal triglyceride transfer protein; TG, triglycerides; hs-CRP, high-sensitivity C-reactive protein; FH, familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia.

transient upper-respiratory symptoms.[21,194] The Trial Evaluating PCSK9 antibody in Subjects with LDL Receptor Abnormalities (TESLA) Part B showed that evolocumab 420 mg administered every four weeks reduced LDL-C by nearly 31% in patients with HoFH.[195] The magnitude of response was closely associated with residual LDL-receptor function, with the most pronounced effects observed in receptor-defective genotypes and minimal effects in receptor-negative patients. Long-term follow-up from the Trial Assessing Long Term Use of PCSK9 Inhibition in Subjects with Genetic LDL Disorders (TAUSSIG) confirmed sustained mean LDL-C reductions of about 21% at four years in patients with HoFH, including those undergoing apheresis.[196] Large cardiovascular outcome trials in broader ASCVD populations, such as the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) and the Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (ODYSSEY OUTCOMES), reported a significant 15% relative risk reduction in primary cardiovascular endpoints.[197,198] Post-hoc analyses that included patients with HeFH suggested a reduction in major adverse cardiovascular events with PCSK9 inhibition.[199] The durability of LDL-C lowering in HeFH was further supported by long-term extension data, including the ODYSSEY Open-Label Extension (ODYSSEY OLE), which reported sustained reductions over several years.[200] Interestingly, neurocognitive safety was also specifically evaluated in the Evaluating PCSK9 Binding antiBody Influence oN coGnitive HeAlth in High cardiovascUlar Risk Subjects (EBBINGHAUS) substudy, which showed no significant cognitive decline with evolocumab over a median 19-month follow-up.[201] Table 8 summarizes major randomized trials of evolocumab and alirocumab in FH.

Furthermore, the clinical benefit correlates with the degree of LDL-C reduction, and guideline panels recommend PCSK9 monoclonal antibodies for very-high-risk FH patients who do not achieve goals on maximally tolerated statin plus ezetimibe or who are statin-intolerant.[21,153-155,157] Research also shows that the response to PCSK9 antibodies depends on residual LDL-receptor function. For instance, patients with null LDLR alleles or receptor-negative HoFH patients generally have minimal or no LDL-C lowering, whereas those with at least one functional allele typically benefit substantially.[160,202,203] Currently, long-term open-label data beyond three years have indicated sustained efficacy and acceptable tolerability of these drugs, although continued monitoring for immunogenicity is warranted.[204]

Inclisiran

Inclisiran is a small interfering RNA (siRNA) that selectively inhibits hepatic PCSK9 synthesis, leading to reduced circulating PCSK9 and increased LDL-receptor availability.[205] The ORION-9 trial evaluated inclisiran alongside statins, with or without ezetimibe, in HeFH patients and demonstrated that inclisiran had an acceptable safety profile and produced an additional 48% reduction in LDL-C.[206] Similar to other PCSK9-directed therapies, the efficacy of inclisiran depends on residual LDL-receptor activity, making it most effective in HeFH and non-null HoFH phenotypes.[207] The ongoing large-scale Heart Protection Study 4/Thrombolysis In Myocardial Infarction 65/ORION-4 (HPS4/TIMI65/ORION4) trial assesses long-term cardiovascular benefits and expanded safety of inclisiran in patients with a prior MI or stroke, and its findings will offer insights into the long-term use of this medication.[21,205] Moreover, the large, randomized placebo-controlled VICTORION-2 PREVENT (VICTORION-2P) trial is currently in progress to evaluate the effects of inclisiran in patients with ASCVD.[208,209] Thus, current guidelines such as the ACC 2022 report recommends inclisiran as an alternative to PCSK9 monoclonal antibodies rather than for combination therapy.[157]

Table 8. Key randomized controlled trials of PCSK9 inhibitors.

Drugs	Trial	Population	Change in LDL-C *vs.* placebo (%)	Change in Lp(a) *vs.* placebo (%)	Change in TG *vs.* placebo (%)
Evolocumab	RUTHERFORD-2	HeFH	−59 to −61	−28 to −32	−12 to −20
	TESLA Part B	HoFH	−31	No change	No change
	TAUSSIG	HoFH (with/without apheresis)	−24*	−14*	—
Alirocumab	ODYSSEY-FH I & II	HeFH	−51 to −58	−18 to −20	−11 to −16
	ODYSSEY HIGH-FH	HeFH with very high baseline LDL-C	−39	−15	−9
	ODYSSEY LONG-TERM	High-risk populations (includes HeFH)	−56	−26	−17
	ODYSSEY OLE	HeFH	−48*	−27*	−2*

*Change reported *versus* baseline. HeFH, Heterozygous familial hypercholesterolemia; HoFH, Homozygous familial hypercholesterolemia; LDL-C, Low-density lipoprotein cholesterol; Lp(a), Lipoprotein(a); PCSK9, Proprotein convertase subtilisin/kexin type 9; ODYSSEY-FH, Efficacy and Safety of Alirocumab in Patients With Heterozygous Familial Hypercholesterolemia (ODYSSEY FH I and FH II); ODYSSEY HIGH-FH, Efficacy and Safety of Alirocumab in Patients With Heterozygous Familial Hypercholesterolemia and Very High Baseline LDL-C (ODYSSEY HIGH FH); ODYSSEY LONG-TERM, Long-Term Safety and Efficacy of Alirocumab in High Cardiovascular Risk Patients With Hypercholesterolemia (ODYSSEY LONG TERM); ODYSSEY OLE, ODYSSEY Open-Label Extension Study; RUTHERFORD-2, Reduction of LDL-C With PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder Study 2; TAUSSIG, Trial Assessing Long-Term Use of PCSK9 Inhibition in Subjects With Genetic Hypercholesterolemia; TESLA Part B, Trial Evaluating PCSK9 Antibody in Subjects With LDL Receptor Abnormalities Part B; TG, Triglycerides.

Bempedoic acid

Bempedoic acid inhibits ATP citrate lyase, an enzyme upstream of HMG-CoA reductase, consequently reducing hepatic cholesterol synthesis and upregulating LDL receptors. This mechanism lowers LDL-C without direct muscle exposure, as the drug is primarily activated in the liver.[207] Randomized controlled trials, including the Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen (CLEAR) HARMONY and CLEAR Wisdom trials, reported LDL-C reductions of approximately 22% in HeFH patients compared to placebo when added to background therapy.[210,211] The CLEAR Outcomes trial further demonstrated a reduction in cardiovascular events among statin-intolerant populations.[212] Phase 3 studies also showed that bempedoic acid reduced LDL-C by ~21% as monotherapy and that fixed-dose combination with ezetimibe produced larger reductions (up to ~36%), with comparable efficacy observed in the HeFH subgroups enrolled in these trials.[213,214] Because bempedoic acid relies on LDL-receptor-mediated clearance, it is effective only when at least one functional LDLR allele is present. Unfortunately, its effectiveness within HoFH remains unestablished.[207] Additionally, regulatory authorizations and guideline recommendations differ by region. Recent multisociety guidance, such as from the ACC 2022 report suggests considering bempedoic acid for additional LDL-C lowering, particularly in statin-intolerant patients, while ESC/EAS panels continue to evaluate emerging outcome data and do not recommended its use in standard practice yet.[157]

VERVE-101

VERVE-101 is an investigational *in vivo* clustered regularly interspaced short palindromic repeats (CRISPR) base-editing therapy designed to introduce permanent, targeted edits in the hepatic PCSK9 *locus*, thus permanently inhibiting PCSK9 production and lowering LDL-C.[215] Preclinical studies in mice have shown sustained LDL-C reduction and acceptable short-term tolerability. Building on these results, interim data from the Phase 1b human trial (VT-1001) demonstrated the first human proof-of-concept for systemic base editing. Among HeFH patients with established ASCVD, a single infusion of VERVE-101 at therapeutic doses resulted in dose-dependent reductions in LDL-C of nearly 39-55%, which were maintained over a 6-month follow-up period.[216]

Bile acid sequestrants

Bile acid sequestrants bind intestinal bile acids and disrupt enterohepatic cholesterol reabsorption, which compels hepatic conversion of cholesterol into bile acids and increases LDL receptor expression to lower plasma LDL-C levels.[21] Hence, these pharmacological agents were often used in the pediatric population as they do not undergo systemic absorption.[160] Older agents, including cholestyramine and colestipol, achieve only modest LDL-C reductions of approximately 10-20% and frequently cause gastrointestinal intolerance, limiting their current use.[160] Colesevelam, a newer and better-tolerated sequestrant, has produced significant LDL-C reductions in pediatric HeFH trials and demonstrated favorable effects on glycemic indices in patients with hyperglycemia, renewing some interest in this class for selected patients and children.[217,218] Nevertheless, sequestrants are rarely used in routine adult FH management due to their limited potency and concerns about tolerability.[21,153]

CETP inhibitors

Cholesteryl ester transfer protein (CETP) inhibitors, such as torcetrapib, dalcetrapib, anacetrapib, and obicetrapib are designed to block the CETP-mediated exchange of cholesteryl esters and triglycerides, thereby increasing HDL-C and altering LDL metabolism.[207,219] Some agents have produced substantial lipid changes in clinical trials. For example, in the REALIZE randomized trial, anacetrapib reduced LDL-C by approximately 40% in HeFH patients when combined with statins.[220] However, the study was discontinued due to concerns regarding anacetrapib getting accumulated in adipose tissues.[207] In contrast, newer CETP inhibitors such as obicetrapib have achieved notable LDL-C reductions of up to 45% without evidence of tissue accumulation and are still under investigation.[221] At the moment, CETP inhibition is not included in standard FH therapy because outcome and long-term safety data remain incomplete.[21,65]

Evinacumab

Evinacumab is a monoclonal antibody that inhibits ANGPTL3, which activates lipoprotein and endothelial lipases to enhance the catabolism of triglyceride-rich particles and decrease downstream LDL production.[207] In a randomized trial involving HoFH patients, evinacumab produced substantial LDL-C reductions (~49% compared to placebo) regardless of the underlying LDLR genotype, with significant reductions observed even in patients with minimal residual LDLR activity.[222] These receptor-independent effects position evinacumab as an important option for refractory HoFH, although its addition into guidelines and patient access vary, and it is not considered a routine first-line agent for HeFH.[21]

Nicotinic acid (vitamin B3)

Nicotinic acid, also called niacin, blocks diacylglycerol acyltransferase-2 in the liver and reduces VLDL secretion. Hence, it lowers LDL-C and increases HDL-C through hepatic effects on apolipoprotein A-I (ApoA-I) synthesis.[223] However, randomized trials have not demonstrated significant cardiovascular benefit, and tolerability remains poor.[224,225] Consequently, niacin formulations are largely unavailable in many regions and are no longer recommended as standard therapy for FH.[21]

Fibrates

Fibrates activate the peroxisome proliferator-activated receptor alpha (PPAR-α), reducing fasting and postprandial triglyc-

erides and remnant lipoproteins, with modest decrease in LDL-C by ≤20% and modest increases in HDL-C by ≤20%.[21,42,226] Outcome data from the Pemafibrate to Reduce Cardiovascular OutcoMes by Reducing Triglycerides IN patiENts With diabeTes (PROMINENT) trial demonstrated reductions in triglyceride-rich lipoproteins but did not show a reduction in cardiovascular events among high-risk populations, leaving the net cardiovascular benefit of fibrates uncertain.[227] Therefore, fibrates have a limited role in routine FH management and are primarily used when triglyceride lowering is specifically indicated.

Resmetirom

Resmetirom is a thyroid hormone receptor-beta-selective agonist. It was recently evaluated in a phase 2 double-blind, placebo-controlled, randomized trial involving 116 HeFH patients and was found that it lowers LDL-C and other atherogenic lipoproteins when used as adjunct therapy, with an acceptable short-term safety profile.[228] Although these preliminary results are promising, larger outcome trials are required before resmetirom can be recommended for routine FH management.

Mipomersen

Mipomersen is an antisense oligonucleotide that targets ApoB-100 messenger RNA, reducing hepatic ApoB synthesis and consequently lowering LDL-C, ApoB, and Lp(a) in HoFH and other severe dyslipidemias.[21,229,230] While clinical development has shown dose-dependent reductions in LDL-C, it has also been associated with frequent hepatic steatosis and elevations in transaminases. Liver biopsy data from early studies showed steatosis without significant inflammation or fibrosis, even with relatively short follow-up periods.[231] Therefore, due to safety and tolerability concerns, mipomersen is not recommended as routine therapy, and its use remains restricted.

Lomitapide

Lomitapide inhibits microsomal triglyceride transfer protein (MTP), blocking the assembly and secretion of ApoB-containing lipoproteins.[42] This results in substantial LDL-C reductions (~50% in HoFH) and may allow for reduced apheresis frequency in severely affected patients.[232] However, lomitapide frequently increases liver aminotransferases and causes hepatic fat accumulation. Its effect on major cardiovascular outcomes remains unproven; therefore, lomitapide is reserved for specialist use in refractory HoFH under close monitoring.[21,232]

Gemcabene

Gemcabene is an oral lipid-modulating agent that acts independently of LDL receptor function by enhancing VLDL clearance and reducing hepatic lipid synthesis and research shows reductions in VLDL cholesterol (VLDL-C), LDL-C, ApoB, triglycerides, and high-sensitivity C-reactive protein (hs-CRP).[233] Preliminary data from the COBALT-1 trial that evaluated the gemcabene's effectiveness in HoFH patients as adjunctive therapy showed LDL-C reductions;[234] however, further clinical development and outcomes evidence are required before gemcabene can be incorporated into standard care.

Non-pharmacological therapies

In addition to pharmacological interventions, FH can be managed through non-pharmacological approaches. The principal non-pharmacological therapies for FH management are summarized in Table 9 (Figure 2).

Table 9. Principal non-pharmacological therapies for familial hypercholesterolemia.

Non-pharmacological therapy	Indication / target population	Typical lipid / clinical effect
Heart-healthy diet	All FH patients as adjunctive therapy. Priority when drug therapy is delayed or not tolerated. Specialist dietetic input for children.	Plant sterols/stanols added to cholesterol-lowering diets reduce total cholesterol and LDL-C by ~0.46–0.62 mmol/L. Omega-3 lowers triglycerides (mean ~0.27 mmol/L). Diet lowers overall cardiometabolic risk beyond LDL-C.
Lipoprotein apheresis	Refractory HoFH and selected severe HeFH not meeting targets on maximal therapy.	Acute LDL-C reduction ~50–75% per session. Lowers cumulative LDL exposure and may regress xanthomas and slow valve/coronary disease progression.
Orthotopic liver transplantation	Selected, refractory HoFH with life-threatening disease unresponsive to other options.	Can correct hepatic LDLR defect and reduce LDL-C by up to ~80% in reported cases.
Genome-editing approaches	Experimental; potential curative strategy for monogenic FH.	Preclinical models show partial restoration of LDLR, LDL-C lowering and reduced atherosclerosis. Human early-phase data are nascent.

FH, Familial Hypercholesterolemia; HeFH, Heterozygous Familial Hypercholesterolemia; HoFH, Homozygous Familial Hypercholesterolemia; LDL-C, Low-density Lipoprotein Cholesterol; Lp(a), Lipoprotein(a).

Heart-healthy diet

A heart-healthy diet serves as an adjunct to pharmacological treatment in FH but does not substitute for lipid-lowering medications in most adults. Dietary intervention is especially important when pharmacotherapy is delayed or not tolerated.[235,236] A meta-analysis of 17 studies (n=376) found that adding plant stanols or sterols to a cholesterol-lowering diet produced consistent reductions in total cholesterol and LDL-C (~0.46 to 0.62 mmol/L), while omega-3 supplements significantly lowered triglycerides (mean difference: 0.27 mmol/L) and showed a non-significant trend toward lower total and LDL-C.[236] However, none of the included trials reported cardiovascular events or mortality. The ESC/EAS recommend introducing a balanced, low-saturated-fat dietary pattern early in life and advise that children with FH receive specialist dietetic supervision, with consideration of statin therapy from approximately 6 to 10 years of age.[21] Additionally, diet influences both direct lipid exposure and traditional cardiometabolic risk factors such as blood pressure, glycemia, adiposity, inflammation, and endothelial function. Emphasizing vegetables, fruits, whole grains, legumes, nuts, fish, and unsaturated vegetable oils, while limiting processed meats, refined sugars, and excessive salt, supports primary prevention.[16,21,237-239] Soluble fiber from oats, barley, legumes, fruits, and certain vegetables lowers circulating cholesterol and represents a practical adjunct to therapy.[240-243]

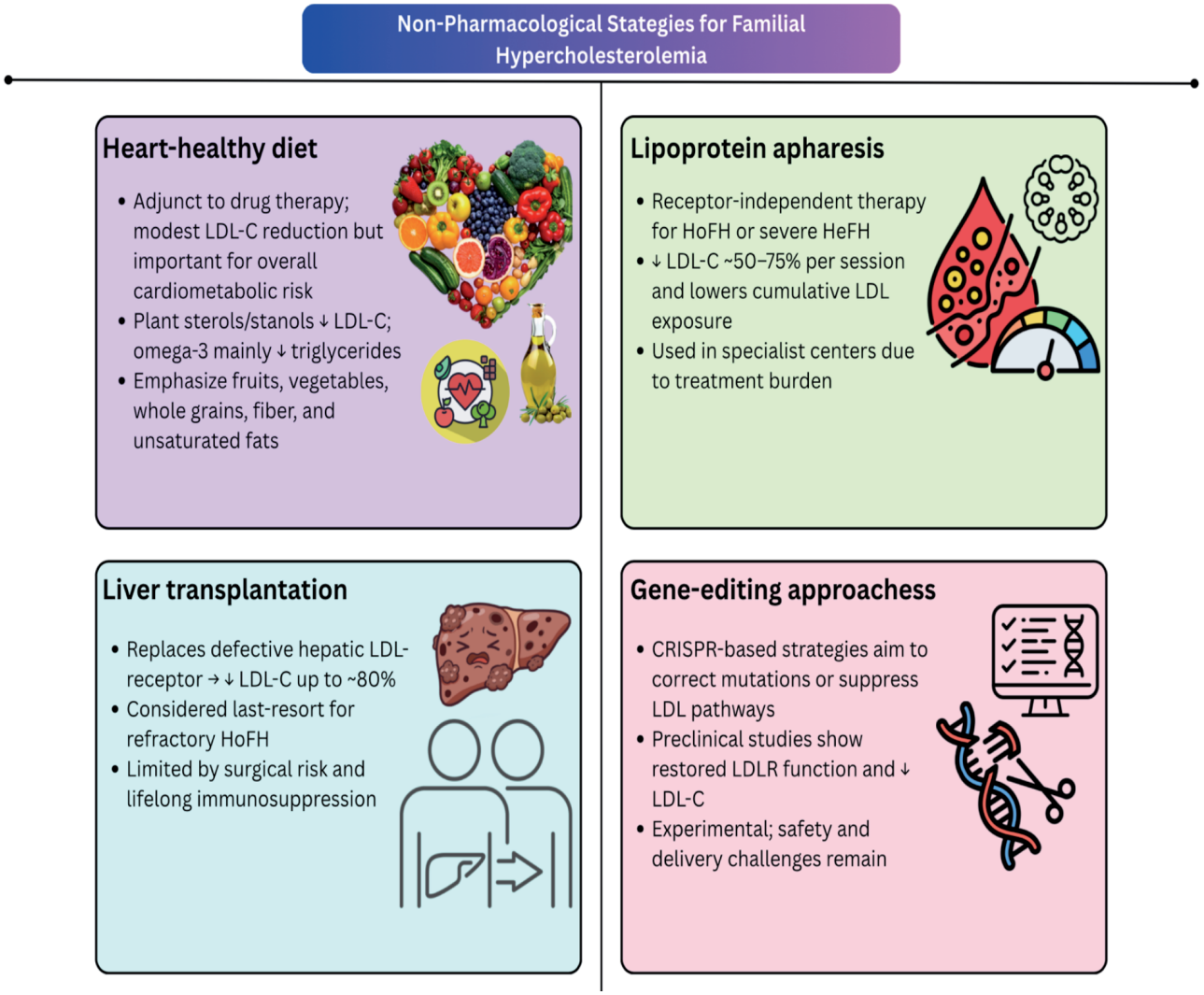

Figure 2. Non-pharmacological therapies.

LDL-C, low-density lipoprotein; HoFH, homozygous familial hypercholesterolemia; HeFH, heterozygous familial hypercholesterolemia; LDLR, low-density lipoprotein; CRISPR, clustered regularly interspaced short palindromic repeats.

Lipoprotein apheresis

Lipoprotein apheresis is an effective, receptor-independent therapy for patients with HoFH and for selected patients with severe HeFH who do not achieve LDL-C targets despite maximal tolerated pharmacotherapy.[44,233,244,245] The procedure acutely reduces circulating LDL-C by approximately 50 to 75% per session. With repeated treatments, it lowers cumulative LDL exposure, improves endothelial function, and may slow or reverse the progression of aortic and coronary lesions as well as tendon xanthomas.[42,160,246-248] However, functional limitations, such as the need for specialized centers, repeated vascular access, treatment burden, and impact on quality of life, limit its use to specialist programs and patients with the greatest unmet need.[207]

Liver transplantation

In cases of refractory HoFH, orthotopic liver transplantation addresses the primary hepatic LDL-receptor defect and has resulted in substantial reductions in LDL-C, with reports of up to 80% reduction.[249-251] Given the significant operative risks, limited donor availability, and the requirement for lifelong immunosuppression, liver transplantation is considered a last-resort therapy, reserved for exceptional cases after all medical and apheresis options have been exhausted.[251]

Gene-editing approaches

Lastly, emerging genome-editing strategies have the potential to provide a future cure by correcting causal mutations or permanently downregulating key regulators of LDL metabolism. Early preclinical studies using CRISPR-based editing of mutant LDL receptor alleles in mice have demonstrated partial restoration of receptor expression, reductions in LDL-C, and smaller atherosclerotic lesions.[207,252,253] While these findings are promising, they remain experimental, and comprehensive safety, off-target, and delivery assessments are necessary before clinical application in humans can be considered.

Future directions

FH is one of the most common inherited diseases, and its considerable lifetime atherogenic potential and substantial population burden require coordinated advancements in detection, risk stratification, therapeutics, and implementation. Future research must address practical gaps in case-finding by evaluating scalable, real-world strategies such as optimized cascade screening programs, validated electronic health record algorithms, and well-designed pediatric or reverse-cascade pilots. These efforts should also address implementation barriers, including limited access to genetic testing, weak family-tracing infrastructure, low awareness among clinicians and patients, and resource constraints that often hinder cascade screening in low-resource settings. Such strategies should be assessed for cost-effectiveness, uptake, and impact on lifetime LDL exposure. Concurrently, genomics should transition from discovery to clinical application. Efforts to standardize and validate polygenic risk scores, enhance variant curation through functional assays, and integrate whole-genome approaches will help clarify mutation-negative phenotypes and support genotype-informed prevention. Therapeutic priorities include conducting robust randomized outcome trials and registry-linked effectiveness studies to determine the long-term cardiovascular benefits, optimal sequencing, and safety of combination therapies and novel agents, including PCSK9-directed therapies, inclisiran, ANGPTL3 inhibitors, bempedoic acid, and LDL receptor-independent drugs. Additionally, durable approaches such as *in vivo* base editing require rigorous assessment of off-target effects and long-term durability. Parallel initiatives should concentrate on refining biomarkers and imaging modalities, including Lp(a), advanced plaque characterization, and multimodal imaging integrated with machine learning. These progressions will enable clinicians to move beyond single-time LDL measurements toward personalized therapy intensity based on cumulative burden and plaque biology. Finally, implementation science and policy efforts must coordinate on reimbursement, workforce training, registry development, and global partnerships to ensure that innovations result in equitable access to care and sustained care, particularly in low- and middle-income settings.

Conclusions

Familial hypercholesterolemia is a common and highly atherogenic disorder that remains substantially under-diagnosed and undertreated, despite the availability of effective and expanding therapeutic options. The integration of focused case finding and cascade testing with advanced molecular diagnostics and guideline-directed combination therapy can prevent a significant proportion of the premature ASCVD burden associated with FH. New pharmacologic agents and emerging genomic therapies provide the potential for substantial improvements in LDL control and durable correction for selected patients; however, their population-level benefit depends on rigorous outcome data, comprehensive safety evaluation, and broad access. To achieve population health gains from genetic and pharmacologic advances, alignment among clinicians, researchers, payers, and public health systems is required to support scalable screening, validated risk stratification, and equitable implementation, ensuring that individuals with FH receive early diagnosis and lifelong, appropriately intensified LDL-lowering care.

Contributions

All the authors read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest

The authors declare that they have no competing interests.

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