

Genetics and Precision Medicine in Familial Hypercholesterolemia

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ABSTRACT

Elevated levels of low-density lipoprotein cholesterol (LDL-C) define hypercholesterolemia, tying it closely to atherosclerosis and cardiovascular disease (CVD). While lifestyle factors such as diet and lack of exercise can play a major role, genetic determinants often shape how early symptoms appear, how intense they get, and how well treatments work. Familial hypercholesterolemia (FH) affects around 1 in every 250 individuals worldwide and is most commonly caused by mutations in low-density lipoprotein receptors (LDLR), apolipoprotein-B (APOB), or Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) proteins that impair LDL clearance. Due to this, cholesterol stays high from an early age, raising the chances of developing CVD much sooner than usual. Despite its prevalence, FH remains vastly underdiagnosed and undertreated, with over 90% of cases unidentified.

This narrative review summarizes the genetic basis of FH, evaluates how genotypes influence diagnosis and treatment, and assesses the current role of pharmacogenomics and personalized medicine in tailoring hypercholesterolemia management.

Furthermore, the paper evaluates the role of pharmacogenomics and personalized medicine frameworks in tailoring hypercholesterolemia management. By integrating genomic data with clinical and social factors, personalized medicine can improve adherence and help doctors choose the optimal treatment. Yet, ensuring fair implementation of genetic screening and precision therapies becomes a main concern, especially in areas where resources are thin. Moving forward means treating individuals, not averages, without leaving any community behind. Ultimately, advancing the genetic understanding of hypercholesterolemia may help complement standardized treatment approaches with increasingly individualized precision strategies for preventing cardiovascular outcomes.

Keywords: *Hypercholesterolemia; Familial Hypercholesterolemia (FH); Low-Density Lipoprotein Cholesterol (LDL-C); Genetics; Pharmacogenomics; Precision Medicine*

INTRODUCTION

Low-density lipoprotein (LDL) is the main carrier of cholesterol in the blood and plays a key role in the development of diseases such as atherosclerosis. Elevated LDL cholesterol (LDL-C) promotes cholesterol accumulation within arterial walls, leading to inflammation and plaque formation.¹ Elevated LDL-C is one of the most reliable indicators of future risk².

Hypercholesterolemia results from both environmental and genetic factors. Although poor diet, physical inactivity, and obesity contribute to elevated cholesterol, inherited variants strongly influence disease onset, severity, and treatment response. The most common form of inherited hypercholesterolemia is Familial Hypercholesterolemia (FH). FH affects roughly 1 in 250 individuals worldwide and is often caused by changes to the low-density lipoprotein receptor (LDLR) gene¹. This gene is responsible for producing receptors that clear LDL particles from the bloodstream. In individuals with FH, those receptors don't work properly, or aren't there at all, so LDL cholesterol remains elevated from infancy onward. FH shows up either from one mutated allele (heterozygous) or, much rarer, when inherited from both alleles (homozygous)¹. Mutations in certain other genes play a role as well. For example, *APOB* is responsible for making apo-B100, the part of LDL that binds to LDL receptors, or *PCSK9*, which also binds to LDL receptors and speeds up their breakdown inside cells. These genes are important for regulating how LDL cholesterol gets removed³.

Despite its prevalence, FH remains substantially underdiagnosed and undertreated. Diagnosing incorrectly, or delaying diagnosis, can steer treatment off track, particularly when maximal statin therapy doesn't work as expected. Additionally, not all patients with similar LDL-C profiles exhibit equal responsiveness to lipid-lowering drug treatments⁴. Differences in how individuals respond to treatments often trace back to variations in their genes. These variations can influence how drugs are processed, how cells handle cholesterol, or how receptors react. Because many cases go undiagnosed and responses to therapy differ so widely, matching care more closely to individual profiles is less of an option and more of a necessity when managing high cholesterol. Although statins remain the foundation of treatment, differences in genetic background and treatment response highlight the potential value of incorporating additional patient-specific information into clinical decision-making. Advances in pharmacogenomics and precision medicine suggest that integrating genomic information into clinical decision-making may improve drug selection, dosing, and long-term outcomes⁴. However, genotype-guided therapies such as PCSK9 inhibitors or ezetimibe have not been standardized, and prospective clinical evidence remains limited⁵.

This literature review examines the global prevalence of hypercholesterolemia, with a focus on personalized interventions tailored to specific genetic mutations. This paper aims to evaluate the efficacy and accessibility of treatments for FH. Simultaneously, this paper will also address the challenges of equity, cost, and equal, easy access. Ultimately, continued study of the genetic basis of FH may help refine risk prediction, treatment selection, and develop future precision medicine approaches for CVD

prevention.

METHODS

To identify relevant studies for this narrative review, searches were conducted in PubMed, Google Scholar, ScienceDirect, Web of Science, ResearchGate, and Scopus for English-language articles published between 1993 and 2025. Search terms included “familial hypercholesterolemia,” “pharmacogenomics,” “LDLR mutations,” “PCSK9 inhibitors,” “pharmacogenomics of statins,” “precision medicine in lipidology,” “APOB gene mutation,” “PCSK9 gene mutation,” “Simon Broome,” “Dutch Lipid Clinic Network,” “statins,” “heterozygous familial hypercholesterolemia,” “homozygous familial hypercholesterolemia,” “cascade screening,” and “polygenic hypercholesterolemia.” Studies published in the last ten years following international clinical guidelines, landmark clinical trials, and high-impact systematic reviews were given priority. Non-English sources were excluded. Sources were selected based on their relevance to the genetics of FH and the clinical application of personalized medicine. Approximately 60 articles were screened in detail, and 23 were ultimately included in the final synthesis. Table 1 summarizes a list of the most relevant articles that were impactful for this narrative review.

Table 1. Summary of studies and reviews included in this paper

Title	Study authors	Year	Study Type	Key Findings
Familial Hypercholesterolemia	Defesche et al. (2017) ¹ .	2017	Narrative Review/Disease Primer	Review explains that most cases result from mutations in the LDLR gene and less commonly in the APOB and PCSK9 genes; emphasizes the importance of early diagnosis
Familial Hypercholesterolemia: A Literature Review of the Pathophysiology and Current and Novel Treatments	Suryawanshi & Warbhe (2023) ⁵ .	2023	Narrative Literature Review	Examines the genetic basis, pathophysiology, diagnosis, and treatment of FH. Explains how precision medicine and emerging targeted therapies may improve outcomes for FH patient

Clogged Arteries, Safety Net Holes: Treating an Underinsured Patient for Homozygous Familial Hypercholesterolemia with Plasmapheresis	Patel et al. (2024) ¹⁹ .	2024	Case Report	Describes a patient with homozygous familial hypercholesterolemia (HoFH) presenting with extremely elevated LDL-C (~984 mg/dL) and acute coronary symptoms (NSTEMI); emphasizes that in resource-limited settings, plasmapheresis may serve as an effective short-term intervention
Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease	Nordestgaard et al. (2013) ³ .	2013	Consensus statement / clinical guideline review	Estimates that between 14–34 million individuals globally may have FH and emphasizes the associated ~13-fold increased risk of coronary heart disease (CHD) if untreated; supports early and aggressive LDL-C lowering therapy

EPIDEMIOLOGY OF HYPERCHOLESTEROLEMIA

Hypercholesterolemia is a global health crisis with significant geographic and socioeconomic disparities. FH affects roughly 30 million individuals, yet many cases go unnoticed.

Global Prevalence of Hypercholesterolemia

Hypercholesterolemia is one of the most common risk factors for CVD. According to the World Health Organization (WHO), elevated cholesterol is estimated to cause approximately 2.6 million deaths annually and one-third of ischemic heart disease cases globally. Although the prevalence of high cholesterol has declined in many high-income countries because of improved screening, dietary changes, and widespread statin use, rates continue to rise in many low- and middle-income countries as obesity, diabetes, and population aging increase ⁶.

Prevalence of Familial Hypercholesterolemia

FH is the most common inherited disorder of lipid metabolism and one of the most prevalent monogenic diseases. Heterozygous familial hypercholesterolemia (HeFH) affects approximately 1 in 200 to 500 individuals, corresponding to nearly 30 million individuals globally. Homozygous familial

hypercholesterolemia (HoFH) affects approximately 1 in 160,000 to 1,000,000 individuals and is characterized by markedly elevated LDL-C levels from birth². Early identification through lipid screening, genetic testing, and cascade screening of family members is critical for reducing cardiovascular morbidity and mortality.

Demographic and Geographic Disparities

Between August 2021 and August 2023, 11.3% of U.S. adults aged 20 years or older had high total cholesterol, declining from 18.3% in 1999-2000⁷. The downward trend was likely tied to improved screening, statin use, and greater public awareness. FH prevalence also varies due to genetic founder effects. Notably higher frequencies of FH mutations are observed in Afrikaners in South Africa. French Canadians, Lebanese populations, and Ashkenazi Jews. In such cases, the frequency of the heterozygous form can range from 1 in 67 to 1 in 400 individuals. Targeted screening in these populations has improved diagnosis and reduced CVD risk².

Diagnosis and Care Disparities

Men are around three times more likely than women to have low HDL-C (26.6% compared to 8.5%)⁸. Additionally, in lower- and middle-income regions, less developed public health infrastructure makes basic lipid testing inaccessible for many. Additionally, in the U.S., there are severe disparities in race and ethnicity. For example, non-Hispanic white adults are less likely to have elevated total cholesterol levels⁸. These inequalities contribute to delayed or inaccurate diagnosis and treatment.

Clinical Expression and Zygosity

The severity of FH is primarily determined by zygosity, which is the genetic composition of the alleles involved (Table 2).

Table 2: Zygosity of Familial Hypercholesterolemia

Feature	Heterozygous FH (HeFH)	Homozygous FH (HoFH)
Genetics	A single mutated allele in a gene (LDLR, APOB, PCSK9)	Two mutated alleles
LDL-C	> 190mg/dL in adults and >160 mg/dL in children Warden et al., 2024) ⁹ . Interpreted alongside other factors.	> 400 mg/dL (can exceed 600 mg/dL)(Warden et al. (2024) ⁹ . Interpreted alongside other factors.
Prevalence	~1 in 200 individuals	~1 in 300,000

Onset	Adulthood (typically)	Infancy and childhood
Statin Response	Generally responsive	Often ineffective due to receptor loss

Individuals with HoFH typically face an aggressive clinical course. Because their cholesterol levels remain extremely high from birth, they often develop cutaneous xanthomas and coronary artery disease (CAD) early. Their LDL receptors nearly completely lose function, and traditional treatments like statins often fail, leading to a significantly poorer prognosis compared to HeFH.

Even though global screening guidelines exist, such as the Dutch Lipid Clinic Network or Simon Broome standards, their implications still vary widely and are inconsistent. Diagnosis often comes only after a life-threatening heart incident, not before. This highlights the urgent need to provide more regular and proactive cascade screening and broader public education and awareness.

GENETIC MUTATIONS IN HYPERCHOLESTEROLEMIA

Genetic mutations are permanent alterations in a DNA sequence that can change the structure, function, or regulation of proteins involved in cholesterol metabolism. In hypercholesterolemia, pathogenic mutations often impair the body's ability to remove LDL-C from the bloodstream. This leads to elevated cholesterol levels and an increased risk of premature CVD (Figure 1). The severity of the phenotype depends on the type of mutation, the mutation's location on the gene, and whether one or both alleles are affected.

Comparative Analysis of Monogenic and Recessive FH Drivers

Hypercholesterolemia's genetic foundations are diverse, with both monogenic and polygenic variations. Monogenic hypercholesterolemia is caused by a pathogenic variant in a single gene that has a major role in LDL clearance. On the other hand, polygenic hypercholesterolemia results from the combined effects of multiple cholesterol-raising genetic variants. These genetic mechanisms affect differences in disease severity, inheritance patterns, and treatment response. The table below (Table 3) outlines the four primary genes implicated in monogenic and autosomal recessive hypercholesterolemia (ARH). It includes physiological products, mechanisms, prevalence, and severity of phenotype.

Table 3: Genes Implicated in Monogenic and Autosomal Recessive Hypercholesterolemia

Gene	Protein Produced	Mechanism of LDL Elevation	Approximate Frequency among FH patients	Typical Clinical Severity
<i>LDLR</i>	Low-Density Lipoprotein Receptor	Disrupts clearance, i.e., null, transport, binding, internalization, or recycling defects	60-90%	Severe to Extreme
<i>APOB</i>	Apolipoprotein B-100	The mutation alters the ligand domain and reduces binding affinity between the LDL particle and the LDLR associated with the liver	Around 5%	Moderate to Severe
<i>PCSK9</i> (GOF)	Proprotein Convertase Subtilisin/Kexin Type 9	Gain-of-function (GOF) mutations resist self-cleavage, increase protein durability, and accelerate the degradation of LDLRs	Around 3%	Severe
<i>LDLRAP1</i>	LDL Receptor Adaptor Protein 1	Autosomal recessive mutations disrupt the adapter function required to internalize the bound LDLR-LDL complex	<1%	Severe

Monogenic Drivers: *LDLR*, *APOB*, *PCSK9*, and *LDLRAP1*

Monogenic FH is primarily due to mutations in four important genes. These include autosomal dominant FH caused by pathogenic variants in *LDLR*, *APOB*, or *PCSK9*, autosomal recessive hypercholesterolemia (ARH) caused by mutations in *LDLRAP1*, and homozygous familial hypercholesterolemia (HoFH).

LDLR: In healthy individuals, the LDL receptor (LDLR) binds and removes low-density lipoprotein cholesterol (LDL-C) from the bloodstream by transporting it into liver cells for processing and recycling. Mutations in the LDLR gene account for 60-90% of FH cases. A range of changes in the LDLR gene splits into null mutations, transport-defective mutations, binding-defective mutations, internalization-defective mutations, and lastly, recycling-defective mutations⁹. Null mutations produce the most severe phenotype, particularly in homozygous FH (HoFH), leading to markedly elevated LDL-C and premature CVD.

APOB: Less frequently (roughly 5% of cases), mutations of a different gene, APOB, can also lead to similar outcomes. This gene is primarily responsible for encoding a key ligand for LDLR called apolipoprotein B-100. Apolipoprotein B-100 is primarily responsible for facilitating the binding of LDL to its receptors on the cell surface. If APOB-100 is mutated, LDL struggles to attach properly, decreasing the removal of LDL particles from the bloodstream. Therefore, LDL-C will accumulate to dangerously high levels.¹⁰

PCSK9: Additionally, scientists identified the role of the *PCSK9* gene in inherited high cholesterol, specifically FH, and discovered an important breakthrough in the understanding of cholesterol regulation. Mutations in *PCSK9* account for approximately 3% of cases. This gene produces a protein made in the liver, which attaches itself to LDL receptors and leads them toward breakdown. With fewer receptors active, less LDL-C gets cleared from the bloodstream. As a result, attention turned sharply to *PCSK9* as a central player in the homeostasis and control of blood lipid levels and a promising point for treatment intervention⁵.

Furthermore, the two primary categories of *PCSK9* variants are gain-of-function (GOF) variants and loss-of-function (LOF) variants.

Gain-of-Function (GOF) variants: GOF variants are relatively rare, occurring in less than 1% of the population, but doctors often detect them among those with FH. *PCSK9* is processed in the Golgi apparatus and can exert its effects either intracellularly or through extracellular secretion. GOF mutations lead to increased binding of *PCSK9* to the LDLR, preventing the receptor from recycling. Instead, the receptor degrades along with its LDL-C and ApoB that it was bound to. Therefore, the clearance of ApoB-100 lipoproteins is impaired, and LDL cholesterol climbs sharply. Consequently, the risk of CVD also increases¹⁰.

Loss of Function (LOF Variants): A loss-of-function (LOF) variant in the *PCSK9* gene reduces the activity of the *PCSK9* protein. Because *PCSK9* normally promotes the breakdown of LDL receptors in the liver, LOF variants allow more LDL receptors to remain on liver cells and remove LDL cholesterol from the bloodstream. As a result, individuals with *PCSK9* LOF variants tend to have lower LDL-C levels and a reduced risk of cardiovascular disease¹⁰. **Autosomal Recessive Hypercholesterolemia (ARH):** Most individuals with FH inherit it through an autosomal dominant pattern; however, a less common form exists that follows an autosomal recessive inheritance pattern. Autosomal recessive

hypercholesterolemia (ARH) occurs when certain proteins, most notably the LDL receptor adaptor protein (*LDLRAP1*), are mutated. Individuals affected by this form have very high LDL-C levels and cardiovascular issues that appear early. Although ARH can be phenotypically similar to HoFH, it is distinct because the LDLR is structurally intact. Instead, the defect lies in receptor internalization rather than the number of receptors or binding affinity. Therefore, ARH is generally associated with slightly less extreme lipid elevations and a somewhat later onset of cardiovascular complications compared with HoFH¹⁰.

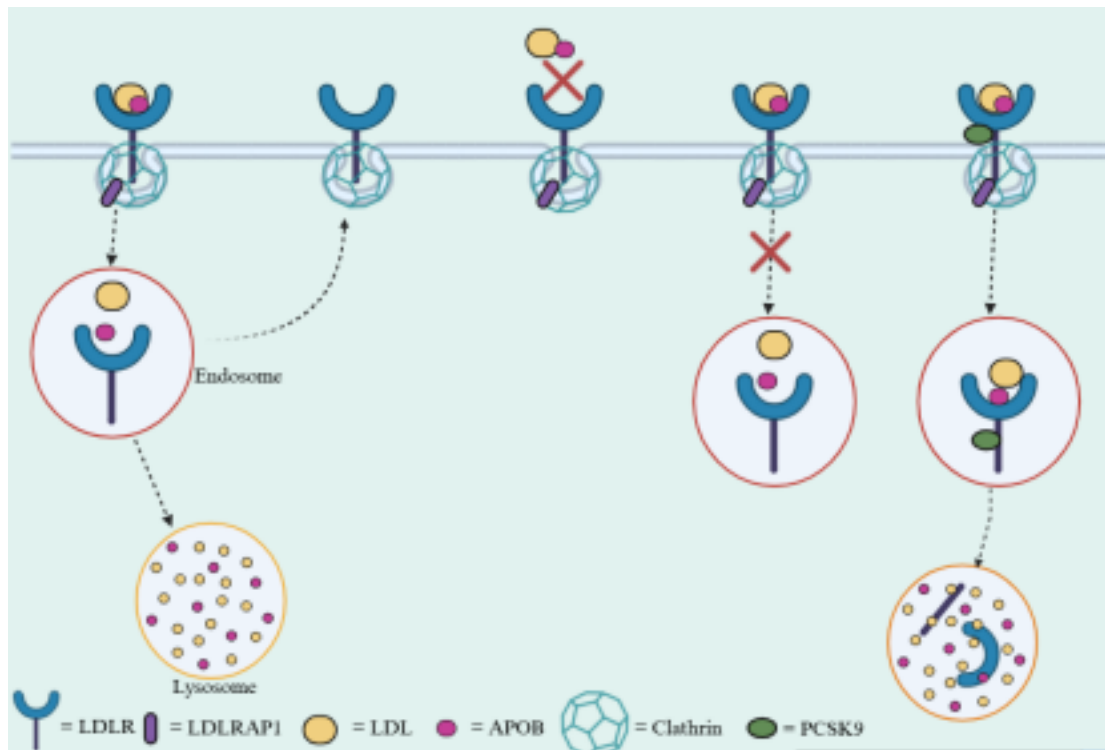


Figure 1. Mechanisms of LDL Receptor Endocytosis, Recycling, and Pathogenic Deficiencies. The Normal Pathway (Left): APOB on the LDL particle binds to the LDLR on the plasma membrane. The adaptor protein LDLRAP1 recruits clathrin to facilitate receptor-mediated endocytosis. Inside the early endosome, the acidic pH causes LDL to dissociate from LDLR. The receptor recycles back to the cell surface, while the LDL particle is transported to the lysosome for enzymatic degradation. Endocytosis Defect (Middle-Left): Loss of the functional adaptor protein LDLRAP1 prevents clathrin recruitment, halting the internalization of the bound LDL-LDLR complex. Binding Defect (Center): Mutations altering the binding domains of either LDLR or APOB prevent ligand-receptor interaction at the cell surface. Internalization Defect (Middle-Right): Disruption of downstream endosomal trafficking halts the internalization process post-clathrin coating. PCSK9-Mediated Regulation (Right): PCSK9 binds to the extracellular domain of LDLR. Upon endocytosis, the presence of PCSK9 locks the receptor-ligand complex, preventing the pH-dependent dissociation of LDLR. Consequently, the receptor is routed away from the recycling pathway and targeted alongside LDL for lysosomal degradation, leading to reduced cell-surface LDLR expression. (Note: This diagram was inspired by a figure from Brautbar et al., 2015)

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(PMID: 25712136) and was created on BioRender.com)

Mutation-Negative and Polygenic Hypercholesterolemia

Standard genetic testing only identifies a monogenic variant in 60-80% of patients with “definite” FH, leaving 20-40% classified as mutation-negative. Researchers hypothesized that these mutation-negative individuals possess polygenic hypercholesterolemia. In polygenic hypercholesterolemia, LDL-C elevations are driven by the cumulative effect of many small effect single-nucleotide polymorphisms (SNPs) rather than a single mutation. Mutation negative patients generally have higher polygenic risk scores (PRS) than healthy individuals and mutation-positive patients. Although polygenic inheritance may explain variability in LDL C levels and cardiovascular risk among individuals with similar mutations, the diagnostic value of PRS alone remains uncertain¹¹.

Treatment Logic

The molecular basis of FH can help explain differences in treatment response. *LDLR*, *APOB*, *PCSK9*, and *LDLRAP1* mutations all elevate LDL-C, yet they do so differently. Receptor-dependent therapies are generally more effective in patients with residual LDL receptor activity. On the other hand, individuals with receptor-negative mutations, particularly those with HoFH, may require receptor-independent therapies. Therefore, genetic information can provide insight into disease mechanisms and potential treatment response. However, genotype-guided selection among newer lipid-lowering therapies is not standardized yet. Additionally, prospective evidence supporting routine genetic selection of specific advanced therapies remains limited.

RISK FACTORS

Genetics

FH is an inherited disorder characterized by lifelong elevation of LDL-C, resulting in accelerated atherosclerosis and premature cardiovascular disease (CVD). Because FH is usually inherited in an autosomal dominant pattern, a family history of markedly elevated cholesterol or early CVD is an important diagnostic clue. Additionally, high lipoprotein(a), often called Lp(a), is a LDL-like particle that can raise CVD risk higher. In individuals with FH, about one out of four also show raised Lp(a), which raises the chances of developing atherosclerosis even further¹.

Environment and Lifestyle Factors

While hypercholesterolemia is more severe when inherited, it can also often be acquired and develop over time. Smoking can further exacerbate disease severity, along with eating foods packed with saturated fats, older age, a sedentary lifestyle, obesity, and insulin problems. The body responds poorly under these

conditions, especially if there is a family history of FH. The risk of myocardial infarction and stroke steeply increases when additional factors accumulate¹.

Complications

Pregnancy causes blood cholesterol to typically climb by 30-50%. Women who have FH might see much larger changes in cholesterol levels. Such shifts often require more careful monitoring, along with adjustments to treatment strategies. Because statins cannot be used while pregnant, keeping LDL-C under control becomes harder¹. Instead of statins, doctors sometimes turn to bile acid sequestrants (discussed later in Treatment Approaches) during pregnancy and breastfeeding because these drugs stay in the gut, do not enter the bloodstream, lower LDL-C effectively, and carry less risk for the fetus¹².

Cardiovascular Disease (CVD) is the leading complication of undertreated hypercholesterolemia. FH accelerates the progression of atherosclerosis, possibly resulting in CAD, early-onset myocardial infarction, peripheral artery disease (PAD), stroke, or aortic valve disease¹. Data from a 2016 study showed that individuals with inherited high cholesterol had double the increase in cholesterol within one year after an acute coronary syndrome, even while using statin drugs, compared to others without the condition¹³. Over time, too many LDL-C particles adhere to vessel linings, triggering inflammation, atheromatous plaque growth, and then cause partial or full blockages within the artery walls. Noticeable buildups of lipid in tissues often show up as pale-yellow patches near the eyes, known as xanthelasmata, or, in younger individuals, as a light ring along the edge of the cornea, known as arcus cornealis. Cholesterol lumps called xanthomas appear as tough, golden nodules, commonly lodging in tendons or beneath subcutaneous tissue. These symptoms strongly support the presence of FH; however, they are only seen in around 15% of cases due to early treatment initiation¹. Individuals with pathogenic LDLR, APOB, or PCSK9 variants have substantially higher coronary artery disease risk than those with similar LDL-C levels but without causative mutations (odds ratio 22.3 to 6.0).¹⁴. Long before adulthood, children with HoFH can experience serious blood vessel diseases, including heart attacks, strokes, and aortic valve dysfunction. Xanthomas may show up between the ages of five and ten. Cholesterol levels often climb past 600 mg/dL, a range considered highly risky. Life expectancy drops sharply during teenage years when care is not sufficient. Elevated LDL-C levels can be inherited; however, the severity can be amplified by lifestyle and biological factors.

DIAGNOSIS

The diagnosis of hypercholesterolemia relies on a combination of methods, such as clinical criteria, lipid profiling, genetic testing, and family history (Figure 2). Timely diagnosis is critical to mitigate cumulative cardiovascular risk.

Lipid Thresholds and Clinical Suspicion

The diagnosis begins with routine lipid profiling. Severe hypercholesterolemia is generally suspected when an adult has over 190 mg/dl of LDL-C but is typically interpreted by family history, clinical signs, and sometimes genetic testing as well. Isolated lipid panels can identify extreme elevations, but they are insufficient on their own. Therefore, clinicians must transition to formal diagnostic frameworks.

Make Early Diagnosis Prevent Early Death (MedPed)

The Make Early Diagnosis to Prevent Early Death (MedPed) criteria represent one of the major clinical approaches used to diagnose FH. This diagnostic system uses age-specific total cholesterol thresholds in combination with family history to assess the likelihood of FH. Because the disorder is inherited in an autosomal dominant manner, individuals with affected relatives have a higher probability of carrying an FH-causing mutation. Therefore, lower cholesterol thresholds are used for those with closer biological relationships to diagnosed individuals. The cholesterol cutoffs were developed from mathematical models based on cholesterol distributions observed in FH populations in the United States and Japan. Validation studies have demonstrated strong diagnostic performance, with a sensitivity of 87% and a specificity of 98% among first-degree relatives of patients with FH. However, a key limitation of the MedPed criteria is that they rely on cholesterol measurements and family history rather than directly identifying the underlying genetic mutation. As a result, genetic testing is increasingly used alongside clinical diagnostic criteria to improve diagnostic accuracy and confirm the molecular basis of the disease².

The Simon Broome System

Another approach is the Simon Broome system, which links LDL-C measurements with tendon xanthomas, inherited patterns of premature CHD, along with genetic evidence to identify cases, labelling them as either "definite" or "probable" FH. Definite FH is when an adult has an LDL-C level of above 193 mg/dL, along with the presence of tendon xanthomas in the patient or a first or second-degree relative or genetic evidence of a mutation. Probable FH is defined by meeting the same lipid threshold with a documented family history of premature coronary heart disease or elevated cholesterol in a relative¹⁵.

The Dutch Lipid Clinic Network (DLCN)

Lastly, like the Simon Broome criteria, the Dutch Lipid Clinic Network scores patients using LDL-C levels, physical symptoms, family history, and genetic findings. When the score reaches eight or above, diagnosis is certain, six to seven points lean toward probable, while three to five points fall into a tentative classification. FH is unlikely when there is less than three points¹⁵.

Genetic Confirmation

Genetic testing is a valuable diagnostic tool for FH, particularly when symptoms do not clearly indicate a

single condition. Identifying pathogenic variants in the LDLR, APOB, or PCSK9 genes provides definitive diagnosis, guides targeted therapy, and reduces diagnostic uncertainty. Whole-exome sequencing (WES) may further improve diagnosis by uncovering hidden genetic causes when conventional testing fails¹⁰. However, 10–50% of clinically diagnosed FH patients remain mutation-negative, suggesting polygenic or undiscovered genetic influences². Although WES is promising for these cases, its high cost, limited accessibility, and complex data interpretation currently restrict widespread use. As sequencing becomes more affordable, it may become a standard tool for diagnosing complex or atypical FH cases.

Cascade Screening

Once an index case (the first family member diagnosed) is identified via clinical or genetic means, cascade screening should be initiated immediately. Cascade screening is another process that can effectively identify individuals with FH. Starting with close family members, then moving to more distant ones, this approach tests relatives of an individual first found to have FH. Because detection happens early, before heart problems appear, it gives time for treatment to start in youth. The cholesterol-only screening strategy uses only LDL-C levels for index cases and relatives and is the least cost-effective strokes¹.

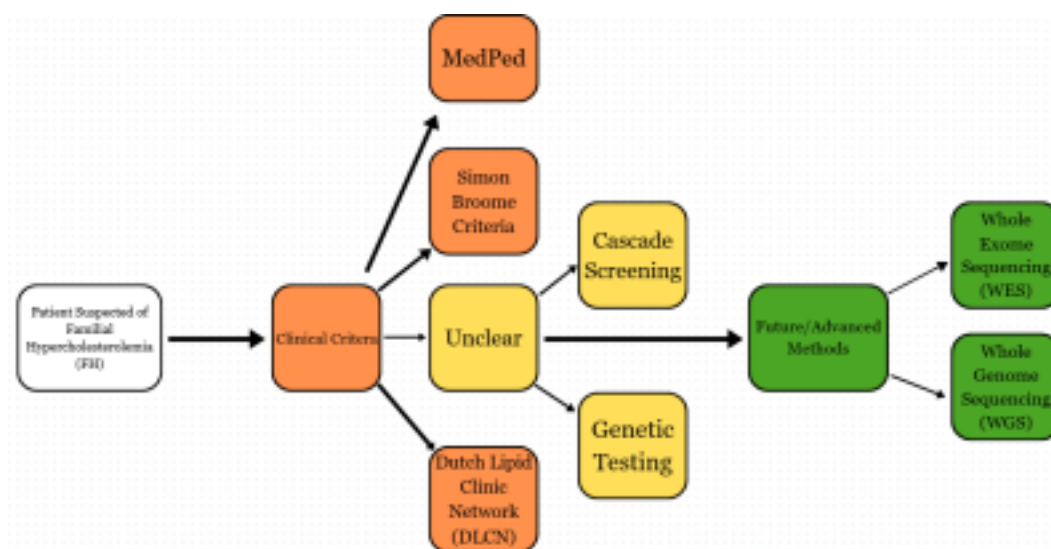


Figure 2. Flowchart illustrating the standardized clinical diagnostic and risk-stratification algorithm for individuals with suspected familial hypercholesterolemia (FH). The clinical workflow proceeds through the initial clinical suspicion, diagnostic criteria scoring, and genetic confirmation.

(Note: this diagram has been drawn for this manuscript from information from various research papers and sources and was created on BioRender.com.)

TREATMENT APPROACHES

Understanding the specific genetic defect is critical for determining the correct therapeutic method.

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Treatments are broadly categorized into mechanisms of action and dependence on LDLR function. This section covers conventional pharmacotherapy (statins, ezetimibe, bile acids sequestrants), monoclonal antibody therapies (PCSK9 inhibitors and evinacumab), RNA-based therapy (inclisiran), lipid-lowering small-molecule therapy (lomitapide), lipoprotein-removal procedures (LDL apheresis and plasmapheresis), and investigational gene-editing approaches (VERVE-101).

Standard and Approved Therapies

These therapies are approved lipid-lowering treatments and form the foundation of routine pharmacological management of FH. Their effectiveness may vary depending on the amount of residual LDL receptor activity.

Receptor-Dependent Therapies

Therapies relying on functional LDL receptors in the liver are central to the treatment of HeFH. However, their effectiveness can be substantially reduced in patients with HoFH who have little or no functional LDL receptor activity.

Statins are the main therapy used to manage high cholesterol levels. By blocking a key enzyme, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, they slow down the amount of cholesterol the body synthesizes. As a result, LDL-C clearance is enhanced due to more active LDL receptors⁵. For individuals with inherited forms of high cholesterol, particularly heterozygous FH, these drugs often bring meaningful reductions when LDLR function is still partially preserved. However, using them long-term may lead to unwanted adverse effects in certain individuals. For example, statin-associated muscle symptoms (SAMS) occur in around 10 to 15% of patients, and there is a 9% increased risk of new-onset diabetes¹⁸.

Ezetimibe works alongside statins, boosting their benefits. It inhibits cholesterol absorption at the border of the small intestine. Adding Ezetimibe can reduce LDL-C by an additional 15 to 20%⁵.

Bile acid sequestrants are another add on treatment. This medicine binds to bile acid and forces the liver to convert more cholesterol into bile acid. Bile acid sequestrants work much like ezetimibe, stepping in if statins fail or cause discomfort⁵.

PCSK9 Inhibition is a more advanced approach and includes drugs such as Alirocumab and Evolocumab. These drugs rely on monoclonal antibodies to stop PCSK9 from degrading LDL receptors⁵. With active LDL receptors still present, patients often see about a 60% drop in LDL C levels¹⁶. Most evidence supporting PCSK9 inhibitors comes from randomized clinical trials in high-risk cardiovascular populations, although long-term genotype-specific data in FH subgroups are limited.

RNA-Based Therapy

Inclisiran is a lipid-lowering therapy that uses small interfering RNA (siRNA) technology to reduce the production of PCSK9 in the liver. By inhibiting PCSK9 synthesis, inclisiran increases the availability of LDL receptors on hepatocytes, enhancing the clearance of LDL-C from the bloodstream. In the Phase 3 ORION-9 trial, which included patients with HeFH receiving maximally tolerated lipid-lowering therapy, inclisiran produced a 39.7% reduction in LDL-C levels compared with placebo and demonstrated consistent efficacy across different FH genotypes. The treatment was generally well tolerated, with adverse event rates like those observed in the placebo group. Inclisiran's infrequent dosing regimen may improve long-term adherence while providing sustained LDL-C reduction in patients who are unable to achieve recommended cholesterol targets with conventional therapies alone¹⁷.

Specialized Therapies for Severe FH and HoFH

These therapies are approved and established treatment options for some patients with severe FH (especially HoFH). However, they are generally used when standard therapies are insufficient or when patients have severe LDLR dysfunction.

Receptor-Independent Therapies

For patients with little to no receptor activity, clinicians must use pathways that bypass the LDLR completely, which reduces the production of cholesterol-carrying particles at the source.

Established LDL Receptor-Independent and Adjunctive Therapies

Individuals who have HeFH usually benefit from taking statins first. However, they usually demonstrate minimal efficacy in HoFH patients. This poor response is a result of the disease's pathophysiology. The statins lower plasma cholesterol by stimulating the expression of hepatic LDL receptors, which are severely deficient in HoFH¹³. If cholesterol levels remain too high, doctors may add other medicines, sometimes including ezetimibe or PCSK9 blockers. Though some newer options exist, like Inclisiran, they tend to work better in one group than the other. Treatment success depends heavily on which form of the condition someone has. Because receptor function is very low, care often needs more than regular medicines. Instead of relying on those alone, options like lomitapide or mipomersen might be considered as these work independently of active LDL receptors, while newer agents such as Angiopoietin-Like Protein 3 (ANGPTL3) inhibitors can join existing regimens⁵.

Evinacumab is a monoclonal antibody and pharmacological therapy that targets ANGPTL3. By inhibiting ANGPTL3, evinacumab promotes lipid clearance through pathways that can reduce LDL-C⁵. Evinacumab is particularly relevant to patients with HoFH, including people with severe LDLR

dysfunction. Importantly, evinacumab doesn't alter or edit DNA. It is a therapy administered to inhibit a circulating protein.

Lomitapide is a small-molecule drug that works by blocking microsomal triglyceride transfer protein (MTP), slowing very low-density lipoprotein (VLDL) release into the blood. This treatment is primarily used for patients with HoFH. However, its clinical use is limited by adverse effects including hepatic steatosis from lipid accumulation and gastrointestinal symptoms⁵. Despite these limitations, reductions in LDL-C may reach nearly 40%, making it useful alongside other treatments for severe cases¹⁸. Like evinacumab, lomitapide is not a gene therapy and does not modify the patient's genetic sequence.

Lipoprotein-Removal Therapies

Lipoprotein-removal procedures are specialized treatments used for patients with severe FH when pharmacological therapy alone does not provide adequate LDL-C control.

LDL Apheresis is a blood purification procedure used to physically remove LDL-C from the bloodstream. Blood is withdrawn from the patient and passed through a filtration system that eliminates LDL particles. The blood is then returned to the circulation. Because LDL-C is directly removed rather than biochemically inhibited, LDL apheresis produces an immediate and substantial reduction in LDL-C levels. However, the effect is temporary and requires repeated sessions to maintain control. It is usually reserved for patients with severe FH⁵.

Plasmapheresis steps in when resources are limited, and full access to LDL apheresis isn't possible. This process pulls out the liquid part of blood, cleans it using filters, and then returns it with replacement fluids. Though it filters plasma broadly and does not target lipids directly, levels may still drop for a while after treatment¹⁹. For individuals with HoFH who gain little benefit from usual drug approaches, this method stands out as highly effective. One report followed a 40-year-old Black man diagnosed with HoFH; his LDL-C reached 984 mg/dL before undergoing two rounds of plasmapheresis. A quick drop in LDL-C became essential ahead of heart vessel imaging. Because it requires fewer resources, plasmapheresis can serve just as well when advanced tools are not at hand¹⁹.

Experimental Genetic Approaches

Unlike the pharmacological and RNA-based therapies described above, gene-editing approaches directly target DNA. They are being investigated as potentially durable treatments for FH. These approaches remain experimental and should be distinguished clearly from conventional drug therapies. Emerging strategies using CRISPR-Cas9 and base-editing technologies aim to permanently change genes relevant to the disease or regulate genes involved in LDL metabolism. In tests with non-human primates, levels of *PCSK9* fell by 84%, LDL-C dropped 60%, and effects held past 200 days²⁰. Yet, worries emerged over unintended edits and rising liver enzyme markers. CRISPR-based gene editing approaches, including VERVE-101 are investigational and are not approved treatments for FH. Early human results are

preliminary, and their long-term safety and effectiveness is still uncertain.

VERVE-101 marks the debut of in-body CRISPR-Cas9 base correction for individuals who have HeFH plus cardiovascular disease. Given once through a vein, it works to silence *PCSK9* for good²¹. Early-phase results have shown reductions in LDL-C in some participants. One patient receiving 0.6 mg/kg showed LDL levels dropped by as much as 55%²¹. In those given 0.45 mg/kg, drops of 39% and 48% appeared, results seen within the top dosage group. These findings show encouraging preliminary evidence that in vivo gene editing may reduce LDL-C in humans. However, they should not be interpreted as established evidence. The small cohort size, early stage of clinical development, limited follow-ups, and uncertainty of the durability and safety of the genetic changes prevent definitive conclusions about VERVE-101's effectiveness.

Translational Barriers and Uncertainties

While these data are promising, they are insufficient to support claims of near-term clinical transformation. Critical scientific and systemic hurdles remain unresolved. For example, current human datasets have small sample sizes and short follow-up durations. Therefore, the long-term durability of the edit and permanent gene silencing is unverified. Additionally, another concern is the risk of genomic edits elsewhere in the sequence. This is a primary safety concern that requires rigorous, multi-year sequencing monitoring.

PERSONALIZED TREATMENTS AND PHARMACOGENOMICS

Current Standardized Approaches and the Emerging Role of Precision Medicine in FH Management

Current FH management relies heavily on standardized treatment approaches, especially statins as the foundation of lipid-lowering therapy. However, disease severity, treatment response, and clinical outcomes vary according to genetic, psychosocial, and environmental factors. Precision medicine seeks to tailor treatment to each person's genetic profile, clinical characteristics, and social context, offering the potential for improved outcomes²³.

Genotype-Phenotype Relationships and Variability in Drug Response

Differences in genes strongly shape how serious a disease becomes and whether treatments work well (Table 4). Individuals with inactive *LDLR* versions usually face worse symptoms and see little benefit from drugs that rely on LDL receptors, but changes in *APOB* disrupt attachment to those receptors and often lead to less intense illness⁴.

Psychosocial, Economic, and Environmental Determinants

Clinical outcomes are influenced not only by genetics but also by psychological, socioeconomic, and environmental factors. Children may demonstrate reduced adherence due to fear of injections or clinical procedures, whereas adults often must balance long-term therapeutic regimens with occupational responsibilities and household obligations. Treatment patterns may also vary according to sex and life stage. In addition, socioeconomic barriers, including high medication costs, expenses associated with procedures such as apheresis, and limited insurance coverage, can substantially restrict access to optimal care. Consequently, patients with similar clinical profiles may exhibit different outcomes depending on trust in healthcare providers, psychological stressors, and competing life demands. Moreover, the meaning attributed to a diagnosis often shapes daily health behaviors more profoundly than statistical risk information alone. Accordingly, flexibility in clinical management is essential, as disease trajectories and definitions of meaningful improvement vary considerably across individuals and contexts.

Risk Evaluation and Decision Making in FH Management

Personalized care also requires flexible clinical decision-making. The Cynefin framework, the somato-psycho-socio-semiotic (SPSS) model, and complex adaptive systems (CAS) theory are general conceptual frameworks from the broader personalized-medicine literature. They have not been validated or established as clinical frameworks specific to FH management, and they are discussed here only as ways of thinking about individualized, context-sensitive care. Pharmacogenomic variants in *SLCO1B1*, *CYP3A4*, *ABCG2*, and *HMGCR* influence statin metabolism, efficacy, and adverse effects, particularly statin-associated muscle symptoms. Although these variants may help guide drug selection and dosing, genetic testing should complement rather than replace clinical assessment⁴.

Pharmacogenomics of Lipid-Lowering Therapies

Alongside current medical and psychological approaches, genetics plays a growing role in how high cholesterol is treated. Changes in genes like *SLCO1B1*, *CYP3A4*, *ABCG2*, and *HMGCR* alter how statins move through the body, work, and cause side effects. For example, in *SLCO1B1*, certain changes slow liver absorption of statins, raising blood levels and increasing the risk of muscle issues. When *CYP3A4* varies, the breakdown of the drug slows down; *ABCG2* differences shift how medicine reaches circulation. Even though *HMGCR* is where statins act directly, gene shifts here affect cholesterol drop, but their impact on heart disease isn't fully mapped yet. Knowing these patterns helps choose which statin to use, adjust amounts, watch for risks, and consider different drugs when needed. Still, gene tests alone cannot reliably prevent future heart issues, meaning real-world decisions must blend DNA findings with patient history and life circumstances²².

Genome-Wide Association Studies and Statin Response Prediction

Genome-wide studies now could show clearer links between inherited differences and how individuals

react to drugs that lower fats in the blood. One look at DNA from more than 18,000 Europeans found several small genetic changes tied to how much bad cholesterol drops when taking statins. Researchers identified key genetic variants near the *SORT1*, *CELSR2*, and *PSRC1* genes, which play important roles in cholesterol transport and LDL receptor regulation²³. Changes like rs646776 and rs12740374 in this group of three genes are linked tightly to stronger decreases in LDL levels after treatment, each shifting results by a tiny but measurable amount. Work on these regions suggests *SORT1* helps control how liver cells take up LDL while also affecting the release of fat-carrying particles. Simultaneously, evidence points to *CELSR2* playing a part in guiding how cholesterol is processed inside²³.

Integrating Pharmacogenomics into Precision Medicine for Hypercholesterolemia

These findings suggest the potential value of more tailored approaches to treating high cholesterol. Genetic testing may help inform treatment decisions by helping doctors gain clarity about who benefits most from statins. Some individuals, due to their genes, may reach target cholesterol levels on smaller doses, reducing the likelihood of adverse reactions. Others, whose genetics suggest limited response, might do better with different drugs like PCSK9 inhibitors or ezetimibe. However, the clinical usefulness of genotype-guided selection of PCSK9 inhibitors, inclisiran, or other advanced therapies remains uncertain. For now, treatment decisions should integrate genetic findings with established clinical factors such as LDL-C levels, cardiovascular risk, and treatment history.

Table 4: Mutation Types and Treatment Response

Mutation Type	Functional Effect	Likely Response to Therapy	Current Clinical Status
<i>LDLR</i> null mutations	Minimal or absent LDL receptor activity	Reduced response to statins and <i>PCSK9</i> inhibitors and may require receptor-independent therapies	Well-established clinical Evidence
<i>LDLR</i> defective mutations	Partial LDL receptor function preserved	Often responsive to statins and <i>PCSK9</i> inhibitors	Established treatment-response evidence; genotype-guided drug selection remains limited
<i>APOB</i> variants	Reduced LDL binding to the receptor	Intermediate response to receptor-dependent therapies	Moderately established evidence; clinical genotype-guided treatment remains limited

<i>PCSK9</i> gain-of function variants	Increased LDLR degradation	Often responsive to <i>PCSK9</i> inhibition	Strong mechanistic evidence; limited evidence for genotype-guided therapy
<i>SLCO1B1</i> variants	Altered statin transport/metabolism	Increased risk of statin associated muscle symptoms	Supported for statin toxicity prediction, not established for newer therapy selection
Polygenic hypercholesterolemia	Multiple small-effect variants	Variable treatment response	Emerging evidence; limited standardization

RECOMMENDATIONS

Improving the detection, management, and outcomes of FH requires integrating genetics, clinical care, and public health interventions. Since over 90% of FH cases remain undiagnosed, expanding early screening and cascade screening should be a public health priority, especially since it is cost-effective¹⁹. FH produces lifelong elevations in LDL-C beginning in childhood, therefore earlier identification is an important opportunity for preventive intervention²⁴. Among all cardiovascular risk factors, elevated LDL-C stands out as one of the most significant and reliable indicators of future risk². Public health campaigns should also promote recognition of FH and encourage earlier testing.

Pharmacogenomic testing has the potential to personalize lipid-lowering therapy, particularly by identifying patients at increased risk of statin intolerance or those most likely to benefit from therapies such as *PCSK9* inhibitors, inclisiran, or receptor-independent agents. However, the genotype-guided selection of these treatments remains investigational rather than standard. More prospective studies are needed to determine if genetic testing improves treatment outcomes and is sufficiently cost-effective for routine clinical use.

Whole-exome sequencing can also identify mutation negative FH and polygenic risk profiles; although their clinical utility is still constrained by cost, variant interpretation challenges, and incomplete genotype-phenotype data¹⁰. Expanding access to genetic testing, advanced therapies, and lipid apheresis through healthcare policy reforms will be essential to ensure equitable implementation of precision medicine. Emerging CRISPR-based therapies also warrant continued investigation²¹.

Continued long-term trials are required to establish safety, durability, and cost-effectiveness of gene-based therapies.[ACTION NEEDED: several numerical claims are still cited to sources that do not support them (see notes to author). Fix these first, then state here that each numerical claim was rechecked

against its source. For VERVE-101, either cite the primary clinical report or state in this response that the early-phase data are cited through a published commentary. Earlier detection, precision therapies, and equitable access will improve outcomes for FH patients and reduce the global burden of CVD.

LIMITATIONS

This narrative review draws on peer-reviewed studies, clinical trials, and international guidelines; however, the strength of evidence varies across topics because the included literature encompasses multiple study designs. Many precision medicine and pharmacogenomic approaches remain investigational, and prospective studies validating genotype-guided therapy are limited. Likewise, CRISPR-based gene-editing therapies are still in early clinical development, with long-term safety, durability, and accessibility yet to be established.

CONCLUSION AND FUTURE DIRECTIONS

Hypercholesterolemia, particularly familial hypercholesterolemia, exemplifies how advances in genetics have transformed the understanding and management of human disease. Research identifying the roles of LDLR, APOB, PCSK9, and LDLRAP1 has revealed the molecular mechanisms responsible for impaired LDL cholesterol clearance. Research has also demonstrated that hypercholesterolemia is a collection of genetically distinct conditions with varying clinical presentations and treatment responses. These discoveries have reshaped diagnostic strategies. Equally important, insights into the genetic basis of hypercholesterolemia have driven the development of increasingly targeted therapies. While statins remain the foundation of treatment, newer agents such as PCSK9 inhibitors, inclisiran, evinacumab, and lomitapide have expanded therapeutic options for patients whose genetic profiles limit the effectiveness of conventional approaches. At the same time, pharmacogenomic research has highlighted how inherited variation can influence both drug efficacy and adverse effects. This shows the importance of individualized treatment strategies. However, genetic information alone cannot fully explain clinical outcomes, as psychosocial, economic, and environmental factors also play critical roles in treatment adherence and long-term disease management. Future research should prioritize larger clinical trials that evaluate genotype-specific treatment outcomes and longer follow-up studies for new therapies. Establishing whether genotype-guided selection of advanced lipid-lowering treatment improves outcomes will be an important step to determine the future role of precision medicine in FH.

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