Recent advances in research and care of familial hypercholesterolaemia

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Heterozygous familial hypercholesterolaemia is a common, autosomal semi-dominant condition characterised by elevation of LDL cholesterol from birth and early onset of atherosclerotic cardiovascular disease. With major advances in knowledge about the disease, familial hypercholesterolaemia has become an exemplar for the practice of precision and personalised medicine. Beyond genetics, developments in clinical risk prediction algorithms and cardiovascular imaging have enabled more accurate risk stratification of patients. Early initiation of cholesterol-lowering therapies can reduce the progression of atherosclerosis and prevent cardiovascular events. Newer treatments offer the possibility of normalising plasma LDL cholesterol concentrations even in homozygous familial hypercholesterolaemia, the most severe form of the condition. Despite these advances, familial hypercholesterolaemia is still inadequately diagnosed and undertreated, with many affected people remaining at high risk of early cardiovascular disease. The application of implementation science to expanding knowledge of familial hypercholesterolaemia has enabled the development and design of potentially more effective models of care. This Review discusses the contemporary knowledge of familial hypercholesterolaemia and its unmet clinical needs.

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Introduction

Familial hypercholesterolaemia is an autosomal, semi-dominant condition characterised by markedly elevated plasma LDL cholesterol concentration from birth, xanthomas, and early onset of atherosclerotic cardiovascular disease (ASCVD).[1] Over the past decade, there have been substantial advances in understanding the genetics,[2] epidemiology,[3–10] and natural history of familial hypercholesterolaemia.[11–13] Clinical algorithms for estimating risk of ASCVD,[12,14] as well as more precise methods for detecting subclinical coronary atherosclerosis,[15,16] have improved risk stratification and paved the way for a more personalised and precise approach to managing care for patients with familial hypercholesterolaemia. The introduction of novel lipid-lowering therapies, especially those aimed at inhibiting proprotein convertase subtilisin/kexin type 9 (PCSK9)[17] and angiopoietin-like protein 3 (ANGPTL3), has also led to potentially better control of hypercholesterolaemia, even in patients with homozygous familial hypercholesterolaemia.[5,18] Despite advances, familial hypercholesterolaemia remains an underdiagnosed and untreated condition, with an urgent need for the design and implementation of effective models of care.[11,19] We review contemporary knowledge of the epidemiology, natural history, genetics, detection and diagnostic methods, risk stratification, and treatment of familial hypercholesterolaemia, as well as implementation strategies for improving care of the condition.

Contemporary epidemiology and natural history of familial hypercholesterolaemia

Population frequency

Although heterozygous familial hypercholesterolaemia was traditionally thought to affect approximately one in 500 individuals in the general population, multiple contemporary epidemiological studies have revealed that this condition is much more common.[7,8,20–23] The gold standard diagnosis of familial hypercholesterolaemia is based on genetic testing, but few studies have systematically assessed its prevalence in wider populations using this method. Such studies tend to support the higher frequency of familial hypercholesterolaemia than previously estimated, as shown by reports from Denmark (between one in 217 to one in 224 individuals)[20] and the UK (between one in 226 to one in 28).[21,22,24]

Two independent large meta-analyses, including 42 and 44 studies (encompassing over 7·3 million and 10·9 million individuals, respectively), concluded that the overall prevalence of heterozygous familial hypercholesterolaemia in the general population is approximately one in 312 individuals.[7,8] As with other genetic conditions, the frequency of familial hypercholesterolaemia varies by ancestry and geographical location,[2] being especially common in closed population subgroups with high rates of consanguinity and genetic founder effects, such as among the Dutch Afrikaners (one in 76 individuals), Christian Lebanese (one in 90), or French Canadians (one in 270).[2] However, significant gaps in knowledge of the prevalence of familial hypercholesterolaemia persist in Africa, Asia, and the Eastern Mediterranean region.

In populations with established ASCVD, the prevalence of heterozygous familial hypercholesterolaemia has been estimated as 10-fold to 20-fold higher than in the general population, particularly among those with premature ASCVD.[7,8] Meta-analyses show hetereozygous familial hypercholesterolaemia affects between one in 16 to 31 patients with coronary artery disease, and one in 75 individuals with stroke.[8,25] These data strongly suggest the need to opportunistically test patients with ASCVD for familial hypercholesterolaemia.[7]

Although heterozygous familial hypercholesterolaemia represents one of the most common monogenic conditions in the general population, homozygous familial

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hypercholesterolaemia is much rarer, occurring in between one in 160 000 and one in 450 000 individuals.[2,26,27] This frequency is, however, higher in communities sharing ascendants or with high rates of consanguinity, indicating the need of robust testing for homozygous familial hypercholesterolaemia.[28,29]

Natural history

Lifelong exposure to elevated LDL cholesterol is the leading cause of elevated ASCVD risk in familial hypercholesterolaemia.[1,30] Severe hypercholesterolaemia (LDL cholesterol concentration higher than 4·9 mmol/L or 190 mg/dL) caused by familial hypercholesterolaemia genetic variants is associated with 22·3-fold increased odds of coronary artery disease compared with individuals who are normolipidaemic.[13] The risk in individuals without familial hypercholesterolaemia-causing variants is nearly four times higher than that associated with severe hypercholesterolaemia in the absence of these variants. Heterozygous familial hypercholesterolaemia in childhood already causes an 11-fold increased relative risk of coronary heart disease in men and a 17-fold increased risk in women aged 25–40 years.[31,32] The introduction of lipid-lowering therapies, especially statins, has led to a notable change in the natural progression of ASCVD in familial hypercholesterolaemia.[33–37] The use of statins was associated with a reduction in the risk of ASCVD events and improved survival.[33–35,37,38]

The most severe form of familial hypercholesterolaemia manifests in its homozygous state.[1,5,6] The survival of patients affected by homozygous familial hypercholesterolaemia is proportional to the amount of cholesterol burden exposure.[36] During a 25-year follow-up of 133 patients with homozygous familial hypercholesterolaemia, the absolute rates of mortality by major adverse cardiovascular events (MACE) were 6·1%, 25·4%, and 50·5%, respectively, in those who reached on-treatment total cholesterol concentrations of <8·1 mmol/L, 8·1–15·1 mmol/L, and >15·1 mmol/L (320 mg/dL, 324–600 mg/dL, >600 mg/dL) respectively.[36] In most situations, except in individuals with a mild phenotype, homozygous familial hypercholesterolaemia is classified as a very high-risk condition, and LDL cholesterol concentration should be intensively reduced through drug combination therapy, lipoprotein apheresis, or both, to prevent ASCVD events and prolong life.[11,29,39] Recently, the publication of large registries[3–6,40–46] and the follow-up of longitudinal cohorts[12,35,47,48] has improved understanding of the contemporary natural history of familial hypercholesterolaemia, acknowledging that many of these patients are on background lipid-lowering therapies, mainly statins.

Familial hypercholesterolaemia is usually diagnosed late in life, on average by age 40 years,[3] and later in women.[44] In the Familial Hypercholesterolemia Studies Collaboration (FHSC) registry with 42 167 adults from 56 countries, ASCVD affected one in five to one in six adults with heterozygous familial hypercholesterolaemia by age 46 years. Of these 42167 patients, 11% had premature coronary artery disease, 59·5% used pharmacological lipid-lowering therapies, and 2·7% had attained LDL cholesterol concentration lower than 1·8 mmol/L (70 mg/dL).[3] Women comprised 56% of participants and were less likely to be treated. Women also had a 2-fold lower frequency of ASCVD overall and early events than men.[3] Of importance, in one study from Norway and the Netherlands, pregnancy and breastfeeding were associated with a 2·3 year loss of statin therapy in women with familial hypercholesterolaemia.[49] In the Spanish Familial Hypercholesterolemia Cohort (SAFEHEART) with 5262 patients with genetically confirmed heterozygous familial hypercholesterolaemia who were undergoing lipid-lowering therapy (54·1% females, mean age 46·1 years, median on-treatment LDL cholesterol 3·0 mmol/L or 120 mg/dL, followed up for a median of 10·3 years), women presented a lower frequency and incidence of ASCVD than men (7·1% *vs* 13·8%).[47] Men had an adjusted 3·5-fold greater risk of events from birth compared with women.[47] A recent meta-analysis of cross-sectional studies on familial hypercholesterolaemia, involving 129441 participants (53·4% females), observed a 2·1-fold to 2·4-fold higher risk of ASCVD events and mortality, respectively, in men.[50] It is essential, however, to emphasise that the risk of ASCVD and early events is greater in women with familial hypercholesterolaemia in comparison to women without the disease,[32] and they should not be discriminated against regarding treatment.[51]

In the FHSC registry, 11848 paediatric patients from 48 countries with heterozygous familial hypercholesterolaemia were diagnosed by age 9 years; 28·5% were using lipid-lowering therapies, and only 25% had controlled LDL cholesterol concentrations <3·5 mmol/L (130 mg/dL).[4] In a 20-year follow-up observational study, Luirink and colleagues[35] showed that statin therapy started at a mean age of 13 years resulted in a reduction in LDL cholesterol concentration by 32% to a mean level of 4·16 mmol/L (166 mg/dL) into adulthood. Compared with their parents, who were not treated until later in life, the children in this cohort showed an increased likelihood of event-free ASCVD survival (1% *vs* 26%) and reduced mortality (0% *vs* 7%). The carotid intima-medial thickness (cIMT), a marker of subclinical vascular disease, in children treated with statins was similar to that of their unaffected siblings. Despite these notable findings, it is important to emphasise that the residual LDL cholesterol concentrations remained very high and might have contributed to delaying the development of ASCVD, but not necessarily preventing it. Evidence from imaging[52] and genetic studies[30] shows a robust association of exposure to a high cholesterol burden with the development of atherosclerosis. Therefore, not only early but also intensive LDL cholesterol lowering would be necessary to cure the disease.

In the Homozygous Familial Hypercholesterolaemia International Clinical Collaborators (HICC) registry, comprising 751 patients (52% female, median age 12 years) from 38 countries, ASCVD, including both coronary artery disease and aortic or supra-aortic valve disease, affected approximately 10% of the study population and occurred 10 years earlier in patients from low-income and middle-income countries (LMICs) compared with those from high-income countries.[5] Notably, evidence from 424 individuals with homozygous familial hypercholesterolaemia has shown a reduction not only in the frequency of aortic valve disease but also in the ratio of supra-aortic to aortic disease in patients undergoing lipid-lowering therapy for homozygous familial hypercholesterolaemia.[53]

In the HICC registry, the mean lowest achieved LDL cholesterol concentrations were 7·5 mmol/L (95% CI 7·1–7·9) or 300 mg/dL (95% CI 284–316), with only 12% of patients overall reaching the LDL cholesterol targets recommended by guidelines (21% in high-income countries and 3% in non-high-income countries).[5] The use of three or more lipid-lowering therapies was higher in high-income countries (66%) compared with non-high-income countries (24%). The use of new and expensive lipid-lowering therapies, such as microsomal triglyceride transfer protein (MTP) and ANGPTL3 inhibitors, was higher in high-income countries, clearly indicating a gap in access to these therapies. However, both the HICC[5] and the US CASCADE registry[42] show that, despite the availability of lipoprotein apheresis and novel therapies, LDL cholesterol persists at elevated concentrations in most patients with homozygous familial hypercholesterolaemia (64 [95%] of 67 patients in the US CASCADE registry).

Notwithstanding the advances in familial hypercholesterolaemia knowledge brought about by these registries and cohorts,[3,5,9,10,12,41] it is important to note that much of the information originates from countries in Europe and the Americas. Therefore, there is still a need for more data to better understand the epidemiology, natural history, genetics, and care models of familial hypercholesterolaemia in regions such as sub-Saharan Africa, Asia, and especially China and India, which have very few reports about the disease.[54,55]

Diagnosing familial hypercholesterolaemia

The diagnosis of familial hypercholesterolaemia should be suspected when LDL cholesterol is elevated (usually above the 95th percentile for age, sex, and country),[11] especially if there is a family history of hypercholesterolaemia or early ASCVD. In adults, LDL cholesterol concentrations typically between 4·9 mmol/L and 10 mmol/L (190–400 mg/dL) are associated with heterozygous familial hypercholesterolaemia, whereas untreated concentrations exceeding 10 mmol/L (400 mg/dL) are more commonly seen in homozygous familial hypercholesterolaemia.[1]

The most accurate way of diagnosing familial hypercholesterolaemia is by genetic testing to identify likely pathogenic or pathogenic variants in the LDL receptor (*LDLR*), apolipoprotein B (*APOB*), and *PCSK9* genes. However, despite advances in molecular biology techniques, genetic diagnosis is still restricted worldwide. Therefore, in most situations, familial hypercholesterolaemia in adults is diagnosed using a combination of phenotypical and laboratory criteria, such as those from the Dutch Lipid Clinic Network,[26] Simon Broome,[56] US Make Early Diagnosis to Prevent Early Deaths (MEDPED),[57] American Heart Association[58] or Japanese Familial Hypercholesterolaemia Criteria,[59] among others.[11] Table 1 shows the phenotypic characteristics of the diverse diagnostic criteria. Unfortunately, the accuracy of these criteria can be compromised by previous use of lipid-lowering therapies, the low frequency of xanthomas, and a lack of information about family history.[4,12,60]

In children and adolescents, the diagnosis of familial hypercholesterolaemia is highly suggested with two measurements of plasma LDL cholesterol concentrations above 4·9 mmol/L (190 mg/dL) alone or 4·1 mmol/L (160 mg/dL) in the presence of a family history of high cholesterol or premature coronary artery disease in the family, or when a parent has a genetic diagnosis, and the child's LDL cholesterol is above 3·5 mmol/L (130 mg/dL).[61] A recent large study conducted in Bavaria found that the modified clinical criteria for adults to predict genetic familial hypercholesterolaemia in children had a sensitivity ranging from 0·44 to 0·54 and specificity from 0·91 to 0·97.[62] The authors concluded that existing clinical diagnostic criteria for familial hypercholesterolaemia in children have a low sensitivity but a high specificity in identifying the condition.[62] Approximately half of true cases with a familial hypercholesterolaemia gene variant were missed in children, supporting the need for revision of clinical practice and the use of genetic testing to increase the precision of early diagnosis.

Genetic basis of familial hypercholesterolaemia

Familial hypercholesterolaemia is an autosomal, semi-dominant condition with two forms: heterozygous or homozygous. In heterozygous familial hypercholesterolaemia, one copy of the altered allele is inherited from only one parent (monoallelic).[29,63] Heterozygous familial hypercholesterolaemia presents a less severe phenotype and can occur due to variants in any of the three familial hypercholesterolaemia-causing genes. In homozygous familial hypercholesterolaemia, both alleles are altered, resulting in a more severe phenotype. Alleles are inherited from each parent (biallelic, with the same variant, previously called true homozygous familial hypercholesterolaemia, or biallelic different variants in the same gene, previously called compound heterozygotes), or, in sporadic cases, the two inherited altered

	LDL cholesterol thresholds, mmol/L	Clinical features	Family history	Genetic testing	Peculiarities
US MEDPED[57]	<20 years, ≥7·0; 20–29 years, ≥7·5; 30–39 years, ≥8·8; 40 years, ≥9·3 (general population)	None required	Adjusted thresholds if familial hypercholesterolaemia is diagnosed in first, second, or third degree relatives	Not required	None
Simon Broome[56]	Adult total cholesterol ≥7·5 or LDL cholesterol ≥4·9; paediatric total cholesterol ≥6·7 or LDL cholesterol ≥4·0	Tendon xanthomas, in index case or in first and second degree relatives	Myocardial infarction in individuals aged <60 years or in first or second degree relatives aged <50 years; or total cholesterol ≥7·5 mmol/L in adult first or second degree relatives or ≥6·5 mmol/L in child or siblings	Not required for definite familial hypercholesterolaemia	Definite: high cholesterol plus xanthomas or positive genetic testing; possible: high cholesterol plus family history of myocardial infarction or high total cholesterol in first or second degree relatives
Japanese (Japan Atherosclerosis Society)[59]	LDL cholesterol ≥4·65	Tendon xanthomata or Achilles tendon ≥9 mm	Familial hypercholesterolaemia or premature coronary artery disease in second degree relatives	Supports but not mandatory	Diagnosis made if ≥2 criteria met
Dutch Lipid Clinics Network[26]	≥8·5, 8 points; 6·5–8·5, 5 points; 4·9–6·4, 3 points; 4·0–4·9, 1 point	Tendon xanthomas (6 points); arcus <45 years (4 points); premature coronary artery disease (2 points); premature peripheral or cerebral vascular disease (1 point)	First degree relative with premature coronary artery disease (1 point); LDL cholesterol higher than 95th percentile (1 point); tendon xanthomas or arcus (2 points); children aged <18 years with LDL cholesterol higher than 95th percentile for age, gender and country (2 points)	Presence of a functional familial hypercholesterolaemia variant in *LDLR*, *ApoB*, or *PCSK9* (8 points)	Definite >8 points; probable 6–8 points; possible 3–5 points; unlikely <3 points
American Heart Association[58]	Heterozygous familial hypercholesterolaemia: LDL cholesterol ≥4·0 for adults and ≥5·0 for paediatric; homozygous familial hypercholesterolaemia: LDL cholesterol ≥10·0; family history of familial hypercholesterolaemia: LDL cholesterol concentration not a criterion; presence of a first degree relative with confirmed familial hypercholesterolaemia	None required	Heterozygous familial hypercholesterolaemia: first degree relative similarly affected or with premature coronary artery disease or with positive genetic testing; homozygous familial hypercholesterolaemia: one or both parents having clinically diagnosed familial hypercholesterolaemia or positive genetic testing for *LDLR*, *APOB*, *PCSK9*, or *LDLRAP*	Not mandatory; diagnosed as heterozygous familial hypercholesterolaemia if positive for LDL cholesterol-raising defect and LDL cholesterol <4·0 mmol/L	Homozygous familial hypercholesterolaemia highly likely if LDL cholesterol ≥14 mmol/L or LDL cholesterol ≥10 mmol/L with aortic valve disease or xanthomata at age <20 years

MEDPED=Make Early Diagnosis to Prevent Early Deaths.

Table 1: **Diagnostic criteria for familial hypercholesterolaemia**

alleles are in different genes (digenic, previously called double heterozygous familial hypercholesterolaemia),[29] for example, *LDLR* and *APOB*. In this last case, both altered alleles can be inherited from just one parent.

Variants in *LDLR* are the most common cause of familial hypercholesterolaemia (>90% of cases). *APOB* variants are present in most countries in about 5–10% of cases and variants in *PCSK9* are rare, only about 1–3% of cases. Other rare recessive disorders present a similar phenotype to familial hypercholesterolaemia (usually named as phenocopies) and are not easily distinguishable clinically, having been described in patients with a familial hypercholesterolaemia phenotype. These rare recessive disorders are sitosterolaemia (*ABCG5* and *ABCG8* genes),[64] lysosomal lipase deficiency (*LIPA* gene), and autosomal recessive hypercholesterolaemia (*LDLRAP1* gene).[63] A unique variant in *APOE* (p.Leu167del) has also been associated with phenotypic heterozygous familial hypercholesterolaemia.[65]

High lipoprotein(a) concentrations have also been associated with the familial hypercholesterolaemia phenotype.[66,67] This association is because the cholesterol in lipoprotein(a) particles is included with LDL cholesterol, either estimated by a direct assay or calculated using standard methods.[68] High lipoprotein(a) concentrations that are strongly determined by variations in the *LPA* gene[69] are independently associated with a greater risk of coronary artery disease[67,70] and aortic valve disease[71] in patients with familial hypercholesterolaemia. Lipoprotein(a) needs to be measured in the index case with familial hypercholesterolaemia, and when elevated, also in relatives to identify affected individuals.

Genetic diagnosis

In most countries, genetic diagnosis of index cases with suspected diagnosis of familial hypercholesterolaemia is performed by different next-generation sequencing techniques, with panel sequencing and exome sequencing being the most used. The recommended panel sequencing should include a minimum of eight genes: the three familial hypercholesterolaemia-causing genes (*LDLR*, *APOB*, and *PCSK9*), two associated genes (*APOE* and *LDLRAP1*), and the three phenocopy genes (*LIPA*, *ABCG5*, and *ABCG8*).[63] If exome sequencing is

performed, at least these eight genes should be analysed and reported. Large rearrangements, such as deletions and duplications of more than one exon, should always be investigated, as they account for approximately 10% of all variants in the *LDLR*.

Variants in *LDLR* can impact the entire LDL receptor cycle, depending on the position within the gene and the specific protein domain affected. Although some protein domains are very well studied, such as the LDL binding domain, for most variants, protein disruption cannot be directly associated with a variant localisation. Functional characterisation is of great importance in determining the residual LDL receptor activity and understanding the severity of the defect, which will impact the hepatic clearance of LDL cholesterol. By using several techniques, it is possible to study the whole LDL receptor cycle, including expression, binding, and uptake, to measure LDL receptor activity.[72] Although there are more than 4000 different familial hypercholesterolaemia variants in ClinVar, a public database of disease variants, only around 20% of variants have been functionally characterised.[73–75] The appendix (p 1) shows the functional classification of LDL receptors and their clinical implications.[76] Although early stop codons and large deletions can be assumed to cause a total loss of function of the LDL receptor, these variants account for only about 30% of all variants.[73] Without functional validation, most variants are classified as variants of unknown significance, meaning they are not actionable and cannot be used in the clinic to improve the prognosis of individuals with familial hypercholesterolaemia.[77] *APOB* variants influence how the LDL particle binds to the LDL receptor, and characterising these variants is essential because *APOB* is a highly polygenic gene, with most variants not linked to disease, even if they are rare.[78] *PCSK9* variants modulate degradation of the LDL receptor and can also be functionally characterised using similar methods as *LDLR* variants. There are two *PCSK9* variants (affecting the same amino acid, Asp374His and Asp374Tyr) associated with a very high ASCVD risk, but the other variants described (<10) do not result in such a severe phenotype.[79]

About 50% of patients with clinical familial hypercholesterolaemia might present with severe hypercholesterolaemia, and no monogenic defects are encountered. In some cases, the phenotype might be due to a polygenic origin. However, the likelihood of finding a monogenic cause increases with a strong phenotype.[80] Despite the current knowledge, other causes should still be sought, as investigating disease mechanisms involving known or new familial hypercholesterolaemia genes.

Some *LDLR* variants have low penetrance, as carriers do not exhibit high LDL cholesterol concentrations.[81,82] In the general population, *LDLR* variants might affect around 2% of carriers;[81] however, these might occur in up to 15% of cases in paediatric populations.[83] Normal LDL concentrations can be due to various modulating factors as being a carrier of an *APOB* or *PCSK9* variant is associated with hypocholesterolaemia or *LDLR* variants could lead to only a slight decrease in LDL receptor activity (10–30% of normal).[63,81,82] Notably, the lower penetrance of loss-of-function variants in *APOB* might also be associated with lower LDL cholesterol concentrations.[63] Age and lifestyle can also influence cholesterol values.[84] However, in these cases, if a pathogenic variant is identified, there is always the need to follow up normocholesterolaemic individuals, especially children and adolescents,[83] for further assessment of potential raised LDL cholesterol concentrations.[11]

Genetic counselling

Genetic testing requires skilled counselling, which entails risk assessment, anticipatory guidance, family-based care, and psychological assessment.[63,85] Patient attitudes towards genetic testing for familial hypercholesterolaemia are generally positive, with there being minimal negative sequelae depending on individual country protections.[86] Counselling is also required when undertaking phenotypic testing of index cases and cascade testing based on cholesterol testing. Given the shortage of trained genetic counsellors, other health-care practitioners, such as nurses and family doctors, might undertake pre-test and post-test counselling after a period of training since familial hypercholesterolaemia is a simple Mendelian disorder. Lipidologists or other related specialists can also perform genetic counselling and, in most cases, are the ones who provide it to the index patient. Complex situations, such as those faced by two parents with heterozygous familial hypercholesterolaemia, should be referred to specialist genetic services for counselling.

See Online for appendix

Screening for familial hypercholesterolaemia

Screening is a prelude to diagnosis. As familial hypercholesterolaemia is under-recognised worldwide,[87] screening to detect those affected is necessary. Familial hypercholesterolaemia meets accepted screening criteria and is evidence-based.[88,89] In the appendix (pp 2–3), we present current strategies, barriers, and facilitators of screening.[90] Many countries have published guidelines for cholesterol testing, with almost all of these recommending, at a minimum, cascade testing of relatives of index cases, and some recommending universal cholesterol testing at a young age (9–11 years).[61,91,92] Modelled data suggest that, to maximise detection of familial hypercholesterolaemia in the population, cascade testing of family members of affected individuals, along with universal screening at a young age, will be required.[93] Implementation of all these recommendations will require testing different models for feasibility, fidelity, adoption, access, reach, cost-effectiveness and sustainability.

Cascade screening

The screening strategy, which has gained the most traction worldwide, is cascade testing of blood relatives of

identified index cases or probands. The Netherlands and Norway have been most successful in this regard. Excellent regional programmes exist in many places around the world where interested parties have organised resources, including genetic testing, processes to simplify notification of relatives, and referral networks.[47,60,89,94] Indeed, cascade screening saves money, as shown in the Netherlands.[95] Paediatric patients living in countries with access to genetic testing, and without other forms of screening, are mostly identified in this manner.[4] A novel use of cascade testing is the identification of parents of identified children.[24,96]

Opportunistic screening

An underutilised strategy is identifying and evaluating patients at a time when the yield might be much higher than in the general population, the presence of a positive test would be actionable, or barriers to screening might be overcome. For high-yield situations, examples of opportunities to screen for familial hypercholesterolaemia include the time of a myocardial infarction in a young patient, the presence of physical findings associated with familial hypercholesterolaemia, or a family history of early heart disease or severely elevated cholesterol.[97] An example of an actionable setting would be testing the spouse of a patient with familial hypercholesterolaemia in peri-pregnancy evaluation, as the fetus could be a homozygote if both spouses have familial hypercholesterolaemia. This situation is most relevant in communities prone to gene founder effects. Adding cholesterol testing to a blood draw panel done for other purposes would remove the barrier of having to obtain a separate blood test, particularly in a child, to accomplish screening. Opportunistic strategies at the general population level include having an alert on a laboratory report to investigate for familial hypercholesterolaemia if LDL cholesterol is above a particular threshold.[98] Testing for hypercholesterolaemia might be considered at the time of blood donation in adults or at newborn screening, with callbacks for levels above actionable LDL cholesterol thresholds.[99]

Universal screening

Universal screening of a given population for elevated LDL cholesterol, typically at some point in childhood, with follow up in those with LDL cholesterol concentrations above an actionable threshold, has been most successful in Slovenia, where testing of children aged 5 years has been conducted for over 20 years.[100] The programme is acceptable (91% of children opt into testing), and about half of those above the LDL cholesterol threshold of 5 mmol/L (200 mg/dL) have a positive test. Universal screening programmes are underway or being developed in other countries, including Germany, Slovakia, and China;[54,62,89,101] however, limited data exist on their current success and specifically their integration with other screening methods. The USA has attempted to implement universal screening for cholesterol in children, but there has been limited uptake, in part due to conflicting guidelines.[88] Limitations of universal screening include false-negative tests in those below the chosen LDL cholesterol threshold and the absence of a strategy for those above the age for universal testing.[102]

Gene-first testing

As the cost of genetic testing decreases, the opportunity for gene-first strategies has emerged. Several settings for this strategy already exist. Wald and colleagues[24] performed universal genetic testing for familial hypercholesterolaemia in children aged 1 year at routine health screening visits. They identified a prevalence of one in 250 children and found that one newly diagnosed adult was identified for every child identified. This study also showed that about 40% of test-positive cases would have been below a threshold chosen for discrimination by LDL cholesterol concentrations. The Geisinger Health System in the USA offered whole-genome sequencing to participants in their health plan, and a prevalence of one in 211 participants was identified, which led to cascade testing of relatives and again helped identify patients below the conventional threshold.[103] The technical feasibility of undertaking newborn genetic screening for familial hypercholesterolaemia has been shown in Australia, but as before, implementation remains a major hurdle.[104] The case for newborn genetic screening for homozygous familial hypercholesterolaemia is stronger than for heterozygous familial hypercholesterolaemia.[105]

Barriers and facilitators for screening

Several barriers and facilitators to familial hypercholesterolaemia screening exist and often impact both the success and failure of the screening strategies presented above. It is useful to consider them at the population, patient, medical care provider, and health-care system levels.[11,87,90,106–108]

At the population level, perhaps the biggest impediment is the lack of prioritisation of prevention as part of a medical encounter, particularly if the event is in the distant future. This absence of emphasis on prevention, coupled with the low awareness of familial hypercholesterolaemia, leads to substantial hesitation from patients with regards to screening. Cost might be a perceived barrier; however, familial hypercholesterolaemia care post-diagnosis is highly cost-effective, as are cascade and opportunistic testing.[109] An absence of protection against genetic discrimination exists in many settings. Government support for familial hypercholesterolaemia care might not be present in some countries.

At the patient level, facilitators include a strong interest in maintaining health and the understanding that cardiovascular health requires control of risk factors. Barriers include the presence of acute and more urgent health issues, cost and ease of familial hypercholesterolaemia screening, lack of perceived

prioritisation of familial hypercholesterolaemia by health-care providers, and guilt associated with the presence of a genetic trait.[90]

At the health-care system level, necessary resources might not be present to support a screening programme, including availability of genetic testing or counselling, lipid specialists, or centralised resources to support cascade testing or other types of notification, such as labelling of laboratory reports or callbacks for LDL cholesterol concentrations above thresholds.[90] Medical care providers might not recognise the importance of making a familial hypercholesterolaemia diagnosis independent of treating LDL cholesterol concentrations to targets, which include the increased risk related to chronic exposure to elevated LDL cholesterol and identifying affected family members.

Special considerations for homozygous familial hypercholesterolaemia

Although any strategy to screen for familial hypercholesterolaemia will identify those with heterozygous familial hypercholesterolaemia, because of increased early morbidity and the existence of new therapies, very early identification of homozygous familial hypercholesterolaemia is of growing importance.[105] The addition of homozygous familial hypercholesterolaemia to existing screening programmes for newborns should be considered. Screening of spouses of patients with known familial hypercholesterolaemia is essential to help with early identification, particularly in communities with gene founder effects. Screening of infants for elevated cholesterol should occur if both parents have a history of severe cholesterol elevations. As discussed above, laboratory report alerts for LDL cholesterol concentrations above 10 mmol/L (400 mg/dL) should also be considered. Given the current low identification rates of familial hypercholesterolaemia,[87] and substantial barriers to improving identification rates, all the screening strategies described above should be implemented in any given setting.

Atherosclerotic cardiovascular disease risk heterogeneity and stratification in heterozygous familial hypercholesterolaemia

In heterozygous familial hypercholesterolaemia the risk of ASCVD is most diverse and depends not only on the LDL cholesterol burden but also on the presence of other risk factors and biomarkers.[1] Over the past decade, substantial advances have been made in understanding ASCVD risk and its biomarkers in heterozygous familial hypercholesterolaemia.[12,14–16,67,70,71,110–112] Figure 1 illustrates the various conditions, risk factors, and biomarkers associated with ASCVD risk in individuals with heterozygous familial hypercholesterolaemia. In the FHSC registry, 23·5% of registry participants smoked, 19·2% had hypertension, 50% had excess body weight BMI ≥25 km/m², and 5% had diabetes.[3]

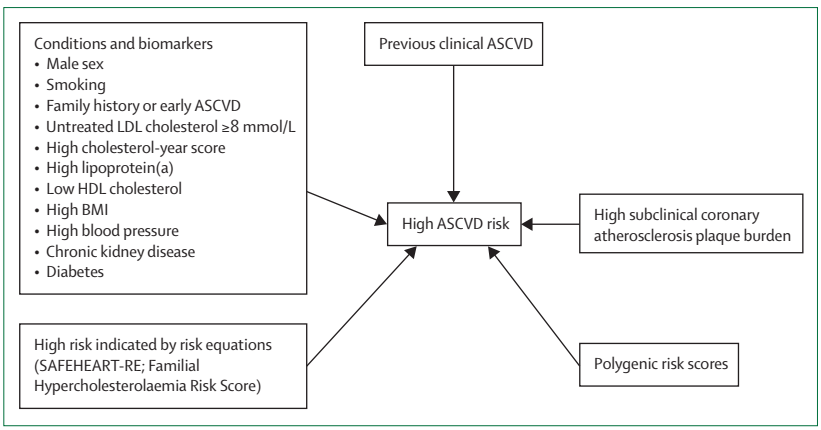

Figure 1: **Risk of ASCVD in heterozygous familial hypercholesterolaemia**
Previous manifestations of ASCVD,[38] especially myocardial infarction and an elevated coronary plaque burden on cardiac CT,[15,16,112] indicate a higher risk for ASCVD events. The risk depends not only on very high LDL cholesterol concentrations or exposure to elevated LDL cholesterol during lifetime, but also on the presence or risk biomarkers like male sex, high lipoprotein(a), low HDL cholesterol, high BMI and blood pressure, family history of early ASCVD, smoking and comorbidities like diabetes and chronic kidney disease.[1] Specific familial hypercholesterolaemia risk equations, such as SAFEHEART-RE[12] and the familial hypercholesterolaemia risk score,[14] can integrate this risk. ASCVD risk might also be modulated by the effect of genes unrelated to lipids, as aggregated in a polygenic risk score.[110,127] LDL cholesterol should always be reduced in patients with familial hypercholesterolaemia. Severe familial hypercholesterolaemia is a clear indication for more intensive LDL cholesterol lowering with PCSK9 inhibitors.[1] ASCVD=atherosclerotic cardiovascular disease.

A history of ASCVD, particularly a myocardial infarction or a substantial burden of subclinical coronary atherosclerosis, indicates a high risk or severe familial hypercholesterolaemia phenotype.[1,15,16,38,112] Extremely high untreated LDL cholesterol concentrations, usually over 8 mmol/L (320 mg/dL), a high cholesterol-year score (reflecting high LDL cholesterol, late initiation of therapy, or both, typically after age 40 years), male sex, early family history of ASCVD events, and risk factors or conditions such as smoking, hypertension, obesity, chronic kidney disease, diabetes, low HDL cholesterol, and elevated lipoprotein(a) concentrations are also independently associated with increased ASCVD risk.[1,12,50,70,113–115] These biomarkers can now be incorporated into specific familial hypercholesterolaemia risk scores, such as SAFEHEART[12] or the familial hypercholesterolaemia risk score.[14] Developed in contemporary familial hypercholesterolaemia populations—most of whom have molecular diagnoses and are receiving statin therapy—these risk equations represent a substantial advance in risk assessment. However, the worldwide generalisation of these risk equations needs to be tested.

In two longitudinal studies, the presence of coronary artery calcification was found to enhance the prediction of ASCVD risk beyond the SAFEHEART equation[16] or classic ASCVD risk factors.[112] Notably, the absence of coronary artery calcification in 2452 patients (mean age 45–54 years at baseline) from Brazil, Japan, France, and Spain, treated with conventional lipid-lowering therapies and maintaining LDL cholesterol concentrations between 2·6 mmol/L and 4·4 mmol/L (104–176 mg/dL), is associated with a very low risk of ASCVD events, as

observed in median follow-ups ranging from 2·7 years to 13·2 years in observational studies.[15,16,112] The 10-year absolute risk of events was 2% in those without coronary artery calcification, although this risk ranged between 2% and 8% per year in those with coronary artery calcification scores greater than 100 Agatston units. These results are consistent with robust observational studies conducted in the general population.[116] Whether the detection of non-calcified coronary plaques, and consequent higher plaque burden not detected by coronary artery calcification, with CT angiography, as seen in 20% of patients with familial hypercholesterolaemia who are asymptomatic for coronary heart disease undergoing statin therapy, will improve risk evaluation over a coronary artery calcification score remains to be determined.[117–119]

The absence or low-intensity of calcification might indicate a plaque phenotype that is more susceptible to modification by anti-atherosclerosis therapies compared with more calcified plaques.[120] Finally, the absence of coronary artery calcification or plaques on CT angiography should not be an argument against starting treatment or for withdrawing LDL cholesterol lowering therapy, especially in younger patients (<40 years) with familial hypercholesterolaemia.[117,121]

Measurement of carotid intima-media thickness (cIMT) by duplex ultrasound has been used to detect early subclinical vascular disease, especially in children and adolescents with familial hypercholesterolaemia. cIMT has been used to gauge the presence and severity of early vascular disease and the impact of lipid-lowering therapies, such as statins and PCSK9 inhibitors.[122–124] In a 20-year follow-up where statin therapy was started in adolescence (mean age 13 years [SD 13·0]) the progression of cIMT over time was similar between treated patients and unaffected siblings.[35] Despite the evidence, due to technical limitations, the routine use of cIMT is not recommended to evaluate ASCVD in paediatric patients with familial hypercholesterolaemia.[11]

Duplex ultrasound can also be used to measure cIMT or detect carotid plaques in adults. A retrospective study from Japan found a strong correlation between a score for carotid disease severity and the extent of coronary artery plaques detected by CT angiography.[112] Both measures were linked to ASCVD events in patients with heterozygous familial hypercholesterolaemia undergoing lipid-lowering therapy. In adults, carotid ultrasonography might be considered to document the presence and extent of atherosclerotic plaque burden and to guide risk assessment.[11]

The risk of ASCVD events has been associated with the severity of the molecular familial hypercholesterolaemia-causing defects and their ensuing elevations in LDL cholesterol.[1,63] Maternal inheritance of familial hypercholesterolaemia variants might result in higher atherosclerosis compared with paternal inheritance due to exposure to elevated LDL cholesterol concentration during pregnancy.[125] ASCVD risk might also be modified by additional LDL cholesterol elevations caused by the effects of polygenes.[126] Additionally, ASCVD risk can be influenced by other genes that predispose individuals to atherosclerosis independently of dyslipidaemia.[110,127] Reeskamp and colleagues[127] have clearly shown an independent association of coronary artery disease polygenic risk scores with ASCVD events in patients from the Netherlands and the UK with molecularly proven familial hypercholesterolaemia. However, these scores need to be tested on heterogeneous populations to show their broad applicability.

Despite the high lifetime risk of ASCVD in heterozygous familial hypercholesterolaemia, some individuals might not develop clinical manifestations even at an older age (≥60 years).[111,128] This has led to the concept of the resilient familial hypercholesterolaemia phenotype[48,111,128] as an alternative to the severe familial hypercholesterolaemia phenotype.[1] The former occurs in the absence of most of these risk biomarkers, whereas the latter includes these risk markers. However, it is essential to emphasise that these phenotypes are mainly described in individuals using conventional lipid-lowering therapies for many years, not including those who eventually died at an early age (<55 years in men and <60 years in women), and that these concepts should be used to personalise the use of more costly cholesterol-lowering treatments, such as the PCSK9 inhibitors.[17,117] These new agents are regrettably not reimbursed or available in LMICs or for individuals without insurance coverage in many high-income countries.[117]

Therapy

Heterozygous familial hypercholesterolaemia

Lifestyle interventions such as adherence to a healthy diet, exercise, smoking cessation, and obesity management are fundamental for managing heterozygous familial hypercholesterolaemia.[11,58] Studies show an association between adherence to Mediterranean or Nordic dietary patterns and lifestyle in comparison with usual diets and lifestyle and improvement in ASCVD risk biomarkers and clinical events.[84,130–132] However, these measures alone often cannot adequately control plasma LDL cholesterol, necessitating the use of pharmacotherapy. Several studies have shown that pharmacological lipid-lowering therapy, even in paediatric patients, reduces the progression[124] or even regresses subclinical vascular disease measured as the cIMT,[122,123] and is associated with a reduction in ASCVD events and mortality.[33–35] Indeed, subgroup analyses of individuals suspected of having heterozygous familial hypercholesterolaemia participating in randomised trials of statins and PCSK9 inhibitors show benefits of these therapies.[37,133,134]

Table 2 shows current therapies for familial hypercholesterolaemia. High-potency statins like atorvastatin and rosuvastatin are preferred, given the need for substantial LDL cholesterol reduction in

	Mechanism of action	Approved for heterozygous familial hypercholesterolaemia	Approved for homozygous familial hypercholesterolaemia	Approved for paediatric use	LDL cholesterol lowering	Typical dose	Common adverse events
Statins	Inhibit HMG-CoA reductase, reducing cholesterol biosynthesis and increasing LDL receptor expression	Yes	Yes	Yes (<6–10 years depending on statin)	25–55%	Atorvastatin 10 mg/day to 80 mg/day, or rosuvastatin 5 mg/day to 40 mg/day	Muscle symptoms, elevated liver enzymes, or new-onset type 2 diabetes
Ezetimibe	Inhibits NPC1L1, reducing intestinal cholesterol absorption	Yes	Yes	Yes (≥10 years)	15–20%	10 mg/day	Gastrointestinal symptoms, or elevated liver enzymes (rare)
Bempedoic acid	Inhibits ATP citrate lyase, upstream of HMG-CoA reductase, reducing cholesterol biosynthesis	Yes	No	No	15–21%	180 mg/day	Hyperuricaemia or liver enzyme elevation
Colesevelam	Bile acid sequestrant; binds bile acids in intestine, increasing LDL receptor activity	Yes	Yes	Yes (≥10 years)	10–20%	3·75 g/day in divided doses	Constipation, gastrointestinal discomfort, increased triglycerides
PCSK9 monoclonal antibodies (eg, alirocumab or evolocumab)	Monoclonal antibodies inhibit PCSK9, increasing LDL receptor recycling	Yes	Yes	Yes (evolocumab ≥10 years; alirocumab ≥8 years)	50–60%*†‡	Alirocumab 75 mg to 150 mg subcutaneously every 2 weeks or 300 mg subcutaneously monthly; evolocumab 140 mg subcutaneously every 2 weeks or 420 mg monthly	Injection site reactions, nasopharyngitis
PCSK9 small interfering RNA (inclisiran)	Small interfering RNA that inhibits PCSK9 synthesis in the liver, increasing LDL receptors	Yes	No	No	50–55%	284 mg subcutaneously on day 1, day 90, and then every 6 months	Injection site reactions or mild influenza-like symptoms
MTP inhibitor (lomitapide)	Inhibits MTP, reducing VLDL and LDL production	No	Yes	No	40–50%	5 mg/day to 60 mg/day based on weight and tolerance	Gastrointestinal side effects, liver enzyme elevation, or hepatic steatosis
ANGPTL3 inhibitor (evinacumab)	Inhibits ANGPTL3, reducing LDL via multiple pathways including increased clearance of VLDL and IDL-indeterminate-density lipoprotein	No	Yes	Yes (≥6 months for homozygous familial hypercholesterolaemia in Europe and ≥1 year in the USA)	40–60%	15 mg/kg intravenously every 4 weeks	Infusion reactions, nasopharyngitis, or headache

HMG-CoA=hydroxy-methyl-glutaryl coenzyme A. *Lower effect might occur in those with homozygous familial hypercholesterolaemia compared with hetereozygous familial hypercholesterolaemia. †LDL cholesterol reduced by 35–40% in paediatric patients.[147,149] ‡Should reduce LDL cholesterol by at least 15% to be continued as treatment in homozygous familial hypercholesterolaemia.

Table 2: **Approved pharmacological lipid-lowering therapies for familial hypercholesterolaemia**[29,39,135,145,148]

familial hypercholesterolaemia.[135] Due to the high ASCVD risk associated with familial hypercholesterolaemia and the exceptionally high LDL cholesterol concentrations, especially in more severe cases and treatment scenarios, it becomes challenging to reach the proposed LDL cholesterol targets with statin therapy alone. For example, only 1·3% of heterozygous familial hypercholesterolaemia patients reached LDL cholesterol concentrations below 1·8 mmol/L (70 mg/dL) with single-drug therapy in the FHSC registry.[3] Therefore, combined statin and ezetimibe therapy should be considered as first-line therapy for these patients.[11,136] Bempedoic acid might provide an additional 21% LDL cholesterol reduction, with lower effects in patients already taking statins.[137] It should be considered as an alternative therapy in adults before the introduction of PCSK9 inhibitors due to its lower cost in some health systems.[11] The following treatment goals should be considered according to the ASCVD risk:[11,138] LDL cholesterol less than 2·5 mmol/L (100 mg/dL) in the absence of ASCVD or other major ASCVD risk factors; LDL cholesterol less than 1·8 mmol/L (70 mg/dL) with imaging evidence of ASCVD alone or other major ASCVD risk factors, and LDL cholesterol less than

1·4 mmol/L (55 mg/dL) with clinical ASCVD. In patients with a recurrent ASCVD event within 2 years while taking maximally tolerated statin treatment, a lower LDL cholesterol goal of less than 1·0 mmol/L (40 mg/dL) might be considered.[11,139] Monoclonal antibodies (alirocumab and evolocumab)[17,140] and small interfering RNA PCSK9 inhibitors (eg, inclisiran)[141] provide on average 50–60% LDL cholesterol reduction in addition to statins, and when available, should be added if cholesterol concentrations remain elevated, especially in patients with severe familial hypercholesterolaemia.[1,117,121]

Homozygous familial hypercholesterolaemia

The management of homozygous familial hypercholesterolaemia relies on early identification and diagnosis, as well as the initiation of therapy as soon as possible, with the rapid addition of additional therapies to bring patients as close as possible to their LDL cholesterol target. Treatment of homozygous familial hypercholesterolaemia requires a specialised team approach, informed by genetic diagnosis, responses to medication, and available resources.[11] Patients with homozygous familial hypercholesterolaemia under 18 years should be treated to an LDL cholesterol target of less than 3·0 mmol/L (115 mg/dL), unless there is clinical or imaging evidence of ASCVD, in which case the target should be lowered similarly to that in heterozygous familial hypercholesterolaemia.[29] Worldwide, the most substantial barrier to optimal care of individuals with homozygous familial hypercholesterolaemia is the limited access to novel therapies or lipoprotein apheresis, particularly in LMICs, leading to poor LDL cholesterol control and increased mortality in individuals at very high risk.[5,6] In addition to a high risk of coronary heart disease, homozygous familial hypercholesterolaemia is also characterised by aortic or supra-aortic valve disease, which also impacts quality of life and survival.[53] The efficacy of LDL cholesterol lowering in homozygous familial hypercholesterolaemia depends heavily on genetic variations and the consequent function of the LDL receptor. Patients affected by variants that result in very low LDL receptor activity (null variants) poorly respond to statins, ezetimibe, or PCSK9 inhibitors (<15% responses in LDL cholesterol) and medications or procedures that act independently of receptors, like lomitapide, evinacumab, or lipoprotein apheresis, will be necessary.[29,39]

Lipoprotein apheresis is a useful adjunctive therapy to control LDL cholesterol and lipoprotein(a) in both adults and children with severe familial hypercholesterolaemia.[11,29] Beyond LDL cholesterol and lipoprotein(a) lowering, lipoprotein apheresis decreases plasma concentrations of inflammatory and thrombotic factors and improves blood viscosity, endothelial function, and microvascular myocardial perfusion.[142] A comprehensive evidence-informed guidance on the use of lipoprotein apheresis in children with homozygous familial hypercholesterolaemia was published in 2024.[143] This guidance also supported the consideration of liver transplantation in children refractory to apheresis and new drug therapies. Liver transplantation is also an option to treat homozygous familial hypercholesterolaemia.[11,29]

Aspects related to pregnancy and breastfeeding

Because pregnancy and breastfeeding interrupt statin therapy, early and intensive treatment is crucial for women with homozygous familial hypercholesterolaemia who can become pregnant.[49] Although the US Food and Drug Administration no longer contraindicates statins in pregnancy,[144] lipid-lowering therapy during this time should be carefully individualised by a multidisciplinary team to balance cardiovascular risk and maternal–fetal safety. New guidelines for pregnancy, breastfeeding, and family planning are required, with research currently underway.[145,146]

Paediatric patients with familial hypercholesterolaemia

Care should focus on the traditional family unit, a multidisciplinary approach, and development of a personalised management plan with careful attention to shared decision making. At diagnosis, all patients should be offered counselling on following a heart-healthy, low-saturated fat, and high-fibre diet, and correcting all other behavioural risk factors for ASCVD. Transitional care strategies are fundamental when moving from paediatric to adult health facilities.[11]

In heterozygous familial hypercholesterolaemia, pharmacological lipid-lowering therapy with statins should be initiated from age 8–10 years for those with LDL cholesterol concentrations higher than 4·9 mmol/L (190 mg/dL). Medications should also be considered for those aged 8–10 years with LDL cholesterol concentrations higher than 4·0 mmol/L (160 mg/dL), in the presence of multiple ASCVD risk factors or a family history of premature ASCVD.[11] For those younger than 8 years and with LDL cholesterol concentrations higher than 4·9 mmol/L (190 mg/dL), pharmacological therapy might also be considered. LDL cholesterol concentrations should be reduced to less than 3·5 mmol/L (130 mg/dL). Combination therapy with ezetimibe or monoclonal PCSK9 inhibitors is an option for severe cases. Early reaching of treatment goals becomes possible since PCSK9 inhibition became available at a younger age; alirocumab from age 8 years[147] and evolocumab from age 10 years.[148,149] Evolocumab treatment not only reduces LDL cholesterol concentrations in paediatric patients with heterozygous familial hypercholesterolaemia but also reduces cIMT.[122]

Homozygous familial hypercholesterolaemia should be treated from diagnosis, independent of age, in paediatric patients.[29] Combination therapy and lipoprotein apheresis are essential for adequate management. Evinacumab, an ANGPTL3 inhibitor in patients aged 5–11 years with homozygous familial hypercholesterolaemia, showed an almost 50% reduction of

the LDL cholesterol concentration within 24 weeks,[150] and has been approved for children with homozygous familial hypercholesterolaemia older than 6 months in Europe and older than 1 year in the USA. Promising data about treatment with lomitapide in childhood have been published,[151] but the medication is not yet approved for paediatric patients despite compassionate use.[152]

Future therapies

Novel therapies are being developed that could be useful for patients with familial hypercholesterolaemia,[153] such as CETP inhibitors,[154] oral PCSK9 inhibitors,[155] adnectins for PCSK9,[156,157] small interfering RNA therapies for ANGPTL3,[158] and CRISPR-based gene or base editing therapies for *PCSK9* and *ANGPTL3*.[159]

Guidelines, models of care, and implementation science

Several clinical guidelines and calls to action have been published over the past decade and are consistent in their recommendations for addressing gaps in care of familial hypercholesterolaemia.[29,58,59,87,139,160] However, few have focused on the application of implementation science and practice.[11,19,161] The International Atherosclerosis Society has developed an evidence-informed guidance that provides a broad and systematic compendium of clinical recommendations for the detection and management of care for patients with familial hypercholesterolaemia, supplemented with implementation strategies to optimise the deployment of models of care.[11]

Several high-quality policy documents have been published and authored not only by familial hypercholesterolaemia experts but also by patient and advocacy groups, providing a higher-level approach to implementation.[63,87,160] The precise effectiveness of these policy documents remains undefined. These efforts have, however, spawned widespread advocacy groups, with success in achieving reimbursement for statin and non-statin drugs for patients with familial hypercholesterolaemia, with the exception of those living in LMICs.[30,87,88,160] The success of national strategies for the genetic detection of familial hypercholesterolaemia has been emphasised in the Netherlands and Norway,[3–5,11] with the Dutch experience illustrating the potential consequences of lack of sustainable funding on the de-implementation of testing and care.[87,95,162] Both Slovenia and Germany have implemented childhood screening programmes,[100,163] but their cost-effectiveness and impact on child–parent screening remains to be shown.[11,102] In England, genetic testing of children aged 2 years at immunisation, followed by child–parent cascade testing, showed promising results in a proof of concept study,[24] but there was poor uptake and yield in a pilot implementation project.[164] Attempts to incorporate testing for familial hypercholesterolaemia in general practice in England appear promising, but there is more implementation practice to do in this important area of family medicine.[165] Although there is substantial implementation research on familial hypercholesterolaemia care in North America, integration and sustainability of models of care are scarce.[106,165] Technology-based and motivational tools to enable detecting and counselling individuals have been well described in these studies, but wider uptake and dissemination remains unclear.[166] Most of the current experience regarding implementation of broader aspects of care for heterozygous familial hypercholesterolaemia has been reported in short-term research projects,[165,166] with no compelling reports of sustainable progress and hard outcome measures. There are only sparse reports from low-income and-middle-income countries, and very few—although increasing—studies from China,[167] likely the country with the largest number of people with familial hypercholesterolaemia. Hence, we rely on more

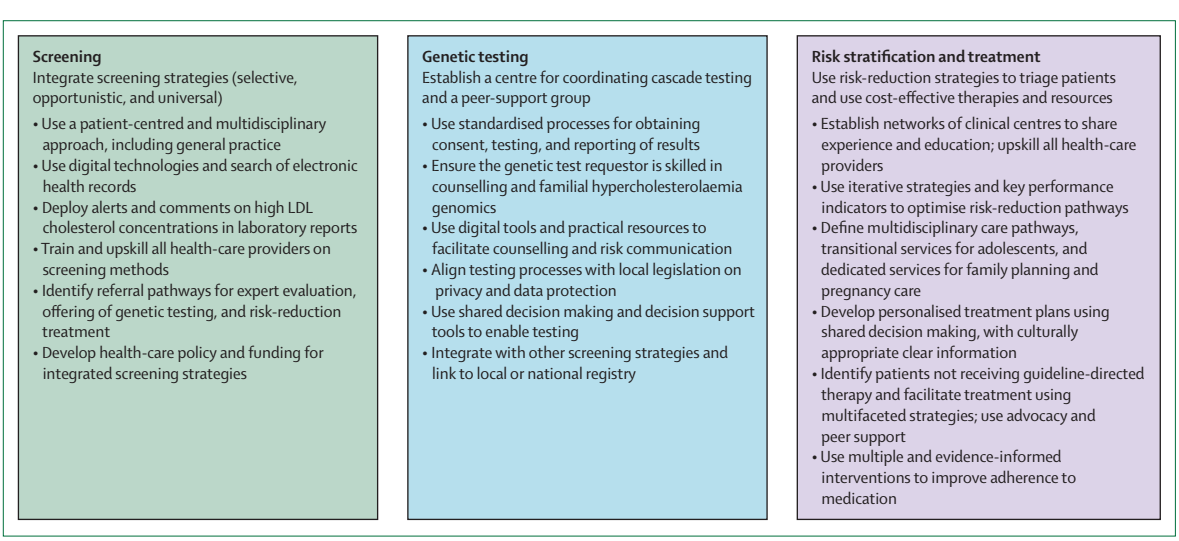

Figure 2: **Implementation recommendations for familial hypercholesterolaemia models of care**[11,19,165]

systematic studies aimed at implementing guidelines regarding care for familial hypercholesterolaemia and should therefore rely on the discipline of implementation science.[168]

Implementation science is a relatively recent scientific method that embodies a new overarching systematic approach for getting the best evidence into clinical practice.[168] The field provides theoretical bases for developing processes and strategies that enable implementation, specifically the adoption, penetrance, scaling, and sustainability of implementation actions. Implementation science uses diverse frameworks for guiding the process, understanding the determinants (eg, barriers and facilitators), and evaluating the outcomes of implementation strategies, some of which have been applied to familial hypercholesterolaemia.

The 2023 guidance from the International Atherosclerosis Society has uniquely promoted implementation science for increasing the impact of clinical recommendations on familial hypercholesterolaemia across the continuum of care. Evidence-informed clinical recommendations (on detection and management) were first developed and classified according to levels of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, followed by identification of context specific

	Population science	Basic science	Life course	Clinical research	Patient-centric	Implementation science
Models of care						
Design country-specific and contextual models of care; develop integrated health systems and academic service partnerships	Design and use clinical quality registries; link to outcome data to understand natural history, sex differences, and treatment effects; and study familial hypercholesterolaemia epidemiology, genetics, and care models in Asia, especially China and India, and sub-Saharan Africa	Perform linkage studies to evaluate gene variants of uncertain significance	Determine natural history using clinical and subclinical ASCVD data; use these findings to guide timing and intensity of treatments; and explore female-specific risk factors for ASCVD, such as pregnancy history	Perform clinical trials with new drugs, including targeting Lipoprotein(a); estimate individual benefit of therapies and revise LDL cholesterol and related lipid targets; and investigate gene editing therapies	Improve knowledge of familial hypercholesterolaemia and promote prevention strategies among communities	Investigate barriers to and enablers of all aspects of care using established frameworks; map these barriers and enablers to multilevel implementation strategies; and make sustainability a priority
Develop models of care involving multidisciplinary teams, including general practice and nurse practitioners	Improve efficiency and integration of different screening methods and diagnostic criteria in diverse populations using age-specific LDL cholesterol values	Identify and evaluate genes in addition to *LDLR*, *APOB*, and *PCSK9*; explore deep intronic regions, and upstream and downstream regions of *LDLR*	Close gaps in guideline-recommended care across ages; focus on children and older adults, including female-specific contexts	Apply multimodal imaging to assess ASCVD in clinical trials; investigate role of in risk stratification, decision making, and designing personalised care plans	Improve patient and family awareness of familial hypercholesterolaemia; explore outcomes for informing value-based care, including achieving treatment goals	Assess implementation practice with frameworks that focus on implementation outcomes; link these with service and patient outcomes; and use interactive strategies to adapt models of care
Explore models of care with emphasis on patient and family experiences of living with familial hypercholesterolaemia and social and economic barriers to care; address concerns about disease, medication, and genetic testing	Undertake pilot screening programme for high Lipoprotein(a) in the context of screening and testing for familial hypercholesterolaemia	Investigate interactions between main gene effects and modifier genes, including polygenic risk scores and lipoprotein(a); apply whole exome or whole genome sequencing approaches	Estimate risk–benefit and cost–benefit of lifelong familial hypercholesterolaemia care; include assessment of treatment goals, long-term benefits, and adverse effects of treatment	Investigate long-term outcome of patients with homozygous familial hypercholesterolaemia treated with lipoprotein apheresis, liver transplantation, and adjunctive and new drugs; undertake studies in countries with gene founder effects and high consanguinity rates	Design adaptive strategies for earlier initiation of treatment, and for improving lifestyle and drug adherence in children and young people	Investigate behaviour change strategies and test these in intervention trials; interventions aimed at individual and collective behaviours to improve adaptive service models of care; use iterative methods to improve sustainability
Develop new frameworks for models of care according to evolving evidence; prioritise models for family planning, pregnancy, and transitional care of adolescents	Resolve barriers to newborn genetic screening and define ethical and funding pathways for implementation	Use existing biobanks with linkage of genomic information to clinical quality registries of familial hypercholesterolaemia patients; study long-term outcomes	Investigate the effect of pregnancy on familial hypercholesterolaemia and the value of LDL cholesterol control in pre-child-bearing women; explore safer methods of hormone replacement therapy and contraception to minimise ASCVD risk	Explore biomarkers to predict early atherosclerosis and drug responsiveness; develop and test country-specific and sex-specific ASCVD risk prediction algorithms, including ASCVD imaging data; explore artificial intelligence models to facilitate familial hypercholesterolaemia diagnosis, risk stratification, and therapy	Develop decision aids to help all individuals participate in screening and subsequent care; adapt approaches based on patient-reported outcome measures and experience measures	Undertake intervention studies that have randomised, stepped-wedge, hybrid, inclusive, and adaptive designs; study patients of different socioeconomic and ancestral backgrounds

ASCVD=atherosclerotic cardiovascular disease.

Table 3: **Proposals for research programmes for familial hypercholesterolaemia**

Search strategy and selection criteria

We focused on the most relevant contemporary aspects of familial hypercholesterolaemia epidemiology, diagnosis and management. A comprehensive literature search was conducted in English using PubMed, focusing on terms related to familial hypercholesterolaemia, including genetics, epidemiology, diagnosis, natural history, cardiovascular risk, therapies, unmet needs, implementation science, and future perspectives. The following terms were searched: "familial hypercholesterolaemia" and "LDLR mutation", "PCSK9 mutation", "APOB", "genetics", "lipoprotein(a)", "diagnosis", "Dutch Lipid Clinic Network", "Simon Broome", "cardiovascular disease", "ASCVD, "risk scores", "therapeutics", "statins", "PCSK9 inhibitors", "lipoprotein apheresis", "ANGPTL3", "models of care", and "implementation science". Emphasis was placed on articles published between Jan 1, 2020 and July 31, 2025.

determinants or influencing factors of change, after which specific implementation strategies (including an assessment of outcomes) were developed by consensus.[11,106] A full list of implementation science recommendations is provided in the International Atherosclerosis Society 2023 guidance for best practices in familial hypercholesterolaemia care.[11,106] The core general and specific implementation strategies are summarised in figure 2.

Future research in familial hypercholesterolaemia

Research can provide high-level evidence that enables the effective use of implementation science for improving context-specific and adaptive models of care for familial hypercholesterolaemia. Table 3 provides an update of selected research topic recommendations, first presented in 2015 and reviewed in 2020,[58,19] covering models of care, population science, basic science, life course, clinical research, patient-centric research, and implementation science. Overall, the most pressing research need is probably in implementation science, noting the persistent gaps in detection, diagnosis and treatment of familial hypercholesterolaemia.[19]

Conclusions

Despite significant scientific and therapeutic advances, familial hypercholesterolaemia remains underdiagnosed and undertreated worldwide.[87] Early detection, especially in childhood, combined with personalised, intensive LDL cholesterol lowering strategies, can substantially reduce ASCVD burden and improve life expectancy. Equitable access to genetic testing and novel therapies is urgently needed, particularly in low-resource settings. Implementation science should now become the focus, guiding the design, evaluation, and scaling of integrated care models. Future research should prioritise closing evidence gaps in diagnosis and treatment, ensuring that all individuals with familial hypercholesterolaemia, regardless of geography, ancestry, or income, benefit from timely, effective, and lifelong care.

Contributors
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