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Evidence-based guidelines

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International Atherosclerosis Society guidance for implementing best practice in the care of familial hypercholesterolaemia

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Abstract

This contemporary, international, evidence-informed guidance aims to achieve the greatest good for the greatest number of people with familial hypercholesterolaemia (FH) across different countries. FH, a family of monogenic defects in the hepatic LDL clearance pathway, is a preventable cause of premature coronary artery disease and death. Worldwide, 35 million people have FH, but most remain undiagnosed or undertreated. Current FH care is guided by a useful and diverse group of evidence-based guidelines, with some primarily directed at cholesterol management and some that are country-specific. However, none of these guidelines provides a comprehensive overview of FH care that includes both the lifelong components of clinical practice and strategies for implementation. Therefore, a group of international experts systematically developed this guidance to compile clinical strategies from existing evidence-based guidelines for the detection (screening, diagnosis, genetic testing and counselling) and management (risk stratification, treatment of adults or children with heterozygous or homozygous FH, therapy during pregnancy and use of apheresis) of patients with FH, update evidence-informed clinical recommendations, and develop and integrate consensus-based implementation strategies at the patient, provider and health-care system levels, with the aim of maximizing the potential benefit for at-risk patients and their families worldwide.

Sections

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Introduction

Familial hypercholesterolaemia (FH) is a co-dominant and highly penetrant monogenic disorder that markedly elevates LDL-cholesterol concentration from birth and, if untreated, leads to premature atherosclerotic cardiovascular disease (ASCVD)[1–3]. FH is a tier 1 genomic condition, meaning that it is a preventable cause of premature disease and death owing to ischaemic heart disease[3–6], with substantial effects on public health[7].

The public health importance of FH is also highlighted by an overall phenotypic frequency in the population of 1 in 311 (refs. 4,8). FH may affect up to 35 million people worldwide, but only 10% are currently diagnosed, and >80% of those treated do not achieve recommended LDL-cholesterol goals[2,9]. The persistent unmet needs in the care of patients with FH have prompted several clinical practice guidelines[10–18], international collaborations[19–22] and global calls to action[9,23–25]. Although new evidence should inform better standards of care[2,26], implementation of guideline recommendations is generally overlooked[27–29].

Implementation science offers the best approach for translating clinical recommendations into routine practice by overcoming barriers to and leveraging enablers of improved care, thereby striving to achieve maximal benefit for the population at risk[29,30]. This approach is highly relevant to the practice of genomics and precision medicine[31]. Therefore, we have promoted this methodology to develop implementation strategies to increase the impact of clinical recommendations on the care of patients with FH[32].

This evidence-informed guidance article provides a systematic compendium of clinical recommendations, informed by best contemporary evidence, for the detection and management of patients with FH. These recommendations are supplemented with general and specific implementation strategies to optimize the deployment in models of care.

Methodology

The full protocol is provided in Supplementary Material 1. Briefly, development of the guidance was led by the International Expert Working Group (IEWG), selected by the board of the International Atherosclerosis Society (IAS) for having diverse expertise in FH (Supplementary Material 1 Appendices 1 and 2). The IEWG defined the scope and focus of the task, developed the evidence evaluation process, appointed a writing committee and sought stakeholder involvement. The development of the clinical guidance was based on previous guidelines that had used evidence-informed recommendations and scored highly on an AGREE-II assessment[33,34] (Supplementary Material 1 Appendix 3).

Design of the guidance

The guidance was generically divided into aspects of detection, management and implementation. Detection covered screening, diagnosis, genetic testing and counselling. Management covered risk stratification, treatment of adults and children with heterozygous FH (HeFH) or homozygous FH (HoFH), management of FH during pregnancy, and use of lipoprotein apheresis. The detection and management sections included preambles, clinical recommendations and implementation recommendations. Clinical recommendations were given classes of recommendation (1 = strong, 2 = moderate and 3 = weak) and corresponding levels of evidence (A = high, B = moderate and C = low)[35,36] (Supplementary Material 1 Appendix 4). Implementation recommendations were developed by consensus, based on relevant published works, and were guided by a framework provided by the Expert Recommendations for Implementing Change (ERIC)[37] (Supplementary Material 1 Appendix 5).

Detection

Screening

FH meets all the criteria for screening for a health-related condition[38,39]. The value of early detection derives from the premise that the burden of ASCVD owing to genetically elevated plasma LDL-cholesterol concentrations in FH begins at birth and accumulates over time[13,40] and that initiation of treatment in childhood can cost-effectively prevent coronary events, improve quality of life and reduce mortality[2,13,40,41].

Early detection of FH is fundamental to all models of care for FH[2,17,23,42]. Detection strategies include opportunistic, selective, systematic and universal screening, using phenotypic and genetic testing, with many of these approaches confirmed as being cost-effective[2,17,42]. However, the best approach to detecting FH in primary care remains uncertain[43–45]. Newer methods have been proposed and evaluated, such as universal screening of children and subsequent child–parent testing[46–49]. Universal screening in the paediatric population has the specific advantage of early detection of HoFH, the most severe type of FH[18]. Population modelling and implementation studies show that, to identify >90% of the population with FH, combining cascade testing of family members of affected individuals with some form of universal screening at younger ages may have the highest potential[42,50,51]. Genomic-based population screening has also been proposed[52], but experience is limited[53–55]. Genomic newborn screening is another option, but remains under investigation[56,57]; enhanced identification of HoFH in populations with a gene founder effect will lead to optimal treatment[1,2,18].

Several barriers to effective screening for FH persist, with implementation practice remaining a major challenge[2,16,24,58–60]. All screening strategies must confer a net benefit for individuals and populations, be socially and culturally acceptable, and be undertaken in accordance with the requirements of the relevant jurisdiction[2,61]. Criteria for effective implementation include feasibility, fidelity, adoption, access and reach, cost–effectiveness and sustainability[62]. Implementation of screening strategies should be underpinned by wide public awareness, comprehensive education and training of health-care professionals, integrated programme management and effective risk-reduction models of care[37]. Population and community support, effective government health policy and public financing are essential, particularly for genomic-based screening programmes[39,52].

The recommendations on screening for FH (Table 1) refer to clinical and public health approaches, supplemented by implementation strategies[37,58,59]. These should be integrated with the recommendations on the diagnosis of FH[2,16,17].

Implementation recommendations on screening for FH

General screening

1. Detection and diagnosis of index cases in the community should ideally use an integrated, patient-centred approach, underpinned by a multidisciplinary strategy involving community and paediatric physicians, obstetric physicians and gynaecologists, nurses and counsellors.
2. Screening and detection strategies should ideally be centrally coordinated, enabling testing by all designated requestors, such as specialist practitioners and genetic counsellors, and linked to a clinical quality registry, particularly when undertaking cascade testing of family members.
3. In countries or regions with limited resources, a skilled health-care professional may lead and coordinate screening and diagnostic strategies, preferably in consultation with a specialist centre and with appropriate training in the care of FH.

Table 1 | Clinical recommendations on screening for familial hypercholesterolaemia

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

ASCVD, atherosclerotic cardiovascular disease; FH, familial hypercholesterolaemia; HeFH, heterozygous familial hypercholesterolaemia; HoFH, homozygous familial hypercholesterolaemia; PCSK9, proprotein convertase subtilisin/kexin type 9.

4. Digital technologies should be used to search electronic health records to enable systematic detection of index cases, particularly in the community care setting.
5. All health-care professionals involved in screening and documentation of the outcome of testing for FH should be adequately trained and fully aware of the local guidance on data protection; this training is particularly important in cascade testing of family members.

Opportunistic screening

6. Opportunistic detection of FH with LDL-cholesterol testing should be performed by dermatologists (for example, on a lipid profile before commencing isotretinoin), rheumatologists and orthopaedic surgeons (for example, for patients having Achilles xanthomas and tenosynovitis), ophthalmologists and optometrists (for example, for patients having premature arcus cornealis, xanthelasma palpebrarum or planar xanthomas), occupational physicians (for example, workplace wellness programmes) and pharmacists (for example, point-of-care testing with a history that is suggestive of FH).
7. Alerts and interpretive comments on laboratory reports of standard lipid profiles should be used to enable case detection, emphasizing the need to make a formal diagnosis and referral for further assessment of FH.

Universal screening

8. Universal screening for FH should be integrated into routine population health surveillance strategies (for example, health checks in adults and community health screening programmes) and prevention procedures (for example, immunization in children).
9. Genetic testing may be considered, if feasible and potentially implementable, for population screening for FH, provided that testing also includes other actionable Centers for Disease Control Tier 1 genetic conditions; the programme should also be equitable, cost-effective and integrated into a well-structured, risk-reduction model of care for FH.
10. Patient support and professional organizations should strongly advocate for health policy to implement universal screening of FH in paediatric populations; this screening is particularly relevant to the early detection of HoFH.

See Box 1 for core implementation strategies.

Diagnosis

The most accurate way to diagnose FH is by genetic testing, which identifies the presence of pathogenic variants that impair LDL receptor function and cause hypercholesterolaemia[2,63,64]. However, genetic testing is currently expensive, not universally available and may not capture all pathogenic variants[2,65–67]. Accordingly, the diagnosis of

FH often relies on phenotypic criteria alone[2,65]. A phenotypic diagnosis of FH may be used to ration genetic analyses by selectively offering testing to potential index cases who are most likely to have a variant; genetic testing may also be offered to patients for whom the presence of a variant could influence treatment recommendations (for example, those with moderately high LDL-cholesterol levels without clinical indicators of FH). Genetic and phenotypic testing are important for both assessing and managing patients with FH[2,13,14,16,17].

Standardizing the phenotypic diagnosis of FH is complicated by the overlap of LDL-cholesterol concentrations between those with HoFH and those with HeFH and between those with HeFH and those with polygenic hypercholesterolaemia[1,2,63]. Diagnostic accuracy also depends on variations in genes unrelated to FH that influence LDL-cholesterol and lipoprotein(a) (Lp(a)) concentrations, as well as on changes in LDL-cholesterol concentrations owing to age, ancestry, menopause, coexisting acute and chronic medical conditions and the environment[2,63]. Adjustment for concurrent treatments that lower LDL-cholesterol concentrations is also required to make an accurate phenotypic diagnosis[17,68].

In adults, the most widely used clinical diagnostic methods are the Dutch Lipid Clinic Network and the Simon Broome criteria[2]; other internationally used methods are the US (MED-PED or AHA), the Japanese and the Canadian criteria[16,69,70] (Supplementary Material 2). However, with statin therapy, the use of clinical criteria alone is more difficult, because those treated from an early age tend not to have physical stigmata, such as tendon xanthomas, and fewer patients will have a positive family history of premature coronary artery disease[2]. Machine learning modelling applied to the diagnosis of FH shows promise[71–73], but requires further evaluation in clinical practice.

In children, clinical diagnosis relies on elevated LDL-cholesterol concentrations and a positive family history of premature coronary artery disease and/or high LDL-cholesterol concentration in at least one parent[13,16,17,74]. In the absence of genetic testing, the diagnosis of FH during cascade testing of adults and children relies on measuring LDL-cholesterol concentrations[17,75].

Box 1

Screening for familial hypercholesterolaemia

Core implementation strategies:

- Integrate screening strategies (selective, opportunistic and universal)
- Use a patient-centred and multidisciplinary approach, including general practice
- Use digital technologies and search of electronic health records
- Deploy alerts and comments on high LDL-cholesterol levels in laboratory reports
- Train and upskill all health-care providers on screening methods
- Identify referral pathways for expert evaluation, offering of genetic testing and risk-reduction treatment
- Develop health-care policy and funding for integrated screening strategies

The clinical diagnosis of HoFH is not as problematic as that of HeFH, because HoFH presents earlier and has a more pronounced clinical phenotype[18,76,77]. However, LDL-cholesterol concentrations can vary in patients with HoFH according to the type of genetic defect and cannot alone establish the diagnosis[18,22,78,79]. Genetically confirmed HoFH can occur in patients with an LDL-cholesterol concentration <13 mmol/l (<500 mg/dl), suggesting that a lower diagnostic threshold of <10 mmol/l (<400 mg/dl) should be used clinically[22,78,79]. Making a phenotypic diagnosis of 'severe FH', on the basis of markedly elevated LDL-cholesterol concentrations and the presence of other major risk factors for ASCVD or a history of ASCVD, may have prognostic value in adults in the absence of a genetic diagnosis[80,81]. The term 'phenotypic' HoFH has also been proposed as an operational diagnosis for patients with the classic phenotype in the absence of detectable biallelic pathogenic, or likely pathogenic, gene variants[18].

When making a clinical diagnosis of FH, the same recommendations as when screening for FH apply to the measurement of LDL-cholesterol concentrations in relation to elevated triglyceride levels, coexistent acute illness and concurrent use of cholesterol-lowering therapies. High Lp(a)-cholesterol concentration associated with very high Lp(a) concentrations may also affect the phenotypic diagnosis of FH in people with markedly elevated Lp(a) concentrations[82–84]. In patients with both phenotypic FH and high Lp(a) concentrations, correcting LDL-cholesterol for Lp(a)-cholesterol may refine the clinical diagnosis and avoid unnecessary genetic testing for FH[82,83,85]. However, how best to accurately adjust LDL-cholesterol for Lp(a)-cholesterol remains unresolved[86,87].

Recommendations for the diagnosis of FH are provided in Table 2.

Implementation recommendations on the diagnosis of FH

1. Cost-effective pathways for making a diagnosis of FH, including referrals to specialists, should be seamlessly integrated with all screening strategies for FH.
2. The diagnosis of FH in children and adolescents should ideally be made by a paediatrician with training and expertise in lipidology, and with attention to assessing the psychological effect of the diagnosis on the family and need to follow regulations on child protection (safeguarding); in those who have difficulty fasting, a non-fasting blood sample may be considered to make a clinical diagnosis.
3. All patients diagnosed with HoFH should be referred to a specialist centre for further physical and psychological assessment and careful planning of care.
4. Whenever possible, all index patients with a phenotypic diagnosis of FH should be offered genetic testing, especially if cascade testing is planned.
5. All health-care professionals involved in making a diagnosis of FH should be aware of the local guidance on data protection.

Genetic testing and counselling: risk notification and cascade testing

Genetic testing refers to an accredited DNA diagnostic methodology with validated bioinformatic analyses performed in a certified laboratory that issues clear reporting of results[88]. Genetic testing in FH increases the precision of diagnosis and counselling, accuracy of risk stratification, adherence to treatment, access to special therapies and cost–effectiveness of cascade testing[1,2,63,64,89,90]. The importance of genetic testing for making a diagnosis of FH is emphasized in two expert statements[91,92]. However, genetic testing is currently underutilized in

Table 2 | Clinical recommendations on diagnosis of familial hypercholesterolaemia

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

ASCVD, atherosclerotic cardiovascular disease; FH, familial hypercholesterolaemia; HeFH, heterozygous familial hypercholesterolaemia; HoFH, homozygous familial hypercholesterolaemia; LDLR, LDL receptor; PCSK9, proprotein convertase subtilisin/kexin type 9.

clinical practice. This underutilization relates to the costs of genetic tests, inadequate clinical skills in genomic medicine, genetic privacy policies, concerns about restrictions on life insurance, and underavailability of genetic counselling services[2,93]. These barriers must be addressed for effective implementation[2,63,93].

Genetic testing aims to provide precise and personalized information that helps clinicians and patients to make informed decisions about their health care[63,88,94]. Accordingly, genetic testing requires skilled counselling, a process that includes risk assessment, anticipatory guidance, family-based care and psychological assessment[63,88,94]. Patient attitudes towards genetic testing for FH are generally positive, given the minimal negative sequelae[95]. A pathogenic DNA variant is often found when FH is suspected clinically[96], but discrepancies include patients with a variant of uncertain significance or a benign variant, patients with no detected pathogenic variant because they have polygenic hypercholesterolaemia or a truly pathogenic variant has not been molecularly identified, and normolipidaemic individuals in whom a pathogenic variant is found[97]. These individuals can benefit from the expertise of a genetic counsellor[1,2,63,88]. More comprehensive genetic testing for pathogenic or likely pathogenic variants will evidently increase the likelihood of making an accurate diagnosis of FH[66,98]. Genetic testing procedures should be standardized, including informed consent, pre-test and post-test genetic counselling, classification of variants, reporting and return of results, follow-up of family members for cascade testing, and shared decision-making[63,94]. A shared decision-making framework uniquely combines the clinical expertise of the health-care provider with the preferences of the patient, personal circumstances, goals, values and beliefs[63,88,94].

Cascade testing is the stepwise, systematic testing of at-risk biological relatives in families with a genetic condition and is strongly recommended for detecting FH[1,2,17,42,63,99]. Cascade testing is highly efficient for identifying additional individuals with FH, particularly younger than the age at diagnosis of the proband[63]. A proactive approach, based on fundamental ethical and legal principles, is most cost-effective[2,17,63]. Cascade testing can be performed genotypically and phenotypically[2,17], but identification of a pathogenic variant (or variants) in the proband allows targeted testing of at-risk relatives with very high sensitivity and specificity[1,63,64]. Cascade genetic testing also identifies relatives who did not inherit the familial variant (variants) and are, therefore, highly unlikely to have FH, an outcome with high personal and clinical utility[63,94]. If index cases with FH are also known to have a high Lp(a) concentration, cascade testing for elevated Lp(a) concentrations should also be considered in first-degree relatives[100]. Reverse cascade testing of parents from a child known to have FH is also recommended[17,63].

Effective and ethical risk notification and cascade testing are underpinned by pre-test and post-test genetic counselling[63,94,99], which may be provided by a health-care professional with expertise in FH and genetics[17]. There are multiple barriers and facilitators that should be addressed to optimize the detection of new cases of FH using cascade testing[29,101–103].

Recommendations for genetic testing and counselling for FH are provided in Table 3 and Fig. 1.

Implementation recommendations on genetic testing and counselling for FH

1. Eligible patients should be referred to a specialized clinic or centre that offers genetic testing and supporting services; direct-to-consumer genetic tests are not recommended or appropriate for clinical use in making a diagnosis of FH.
2. A standardized process for obtaining informed consent for genetic testing should be used, ensuring:
   a. Informed consent considers literacy and level of comprehension and sociocultural and psychological background of the patient, includes a lay explanation of risk, addresses the possible impact of either a positive or negative result and allows the patient to withdraw consent.
   b. Modifications to the process for paediatric patients, specifying appropriate assent be given by a custodial parent or guardian.
3. Sample collection, testing, analyses and reporting of findings should use a standardized process, as follows:
   a. Standardize collection procedures for blood and/or saliva samples.
   b. Carry out testing using a centralized service in a fully accredited laboratory.

Table 3 | Clinical recommendations on genetic testing and counselling for familial hypercholesterolaemia

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

See Fig. 1 for an algorithm for cascade testing of family members. ACMG, American College of Medical Genetics and Genomics; AMP, Association for Molecular Pathology; ClinGen, Clinical Genome Resource; FH, familial hypercholesterolaemia; HeFH, heterozygous familial hypercholesterolaemia; HoFH, homozygous familial hypercholesterolaemia; LDLR, LDL receptor; PCSK9, proprotein convertase subtilisin/kexin type 9.

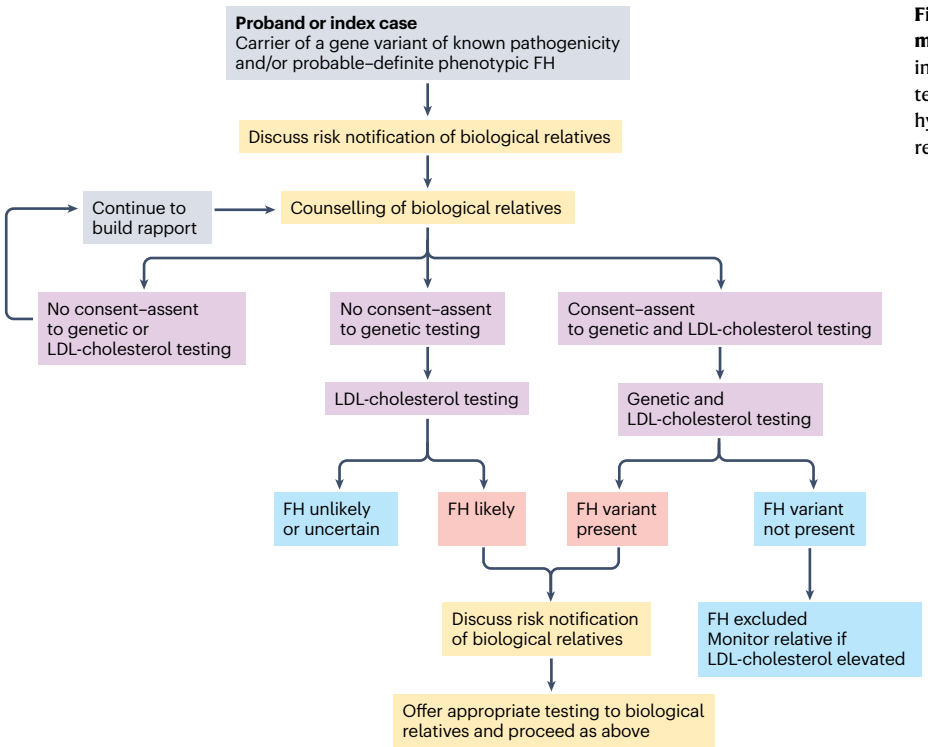

Fig. 1 | Algorithm for cascade testing of family members for familial hypercholesterolaemia. Options include using LDL-cholesterol testing alone or genetic testing together with LDL-cholesterol testing. FH, familial hypercholesterolaemia. Adapted with permission from ref. 17, Elsevier.

c. Apply validated bioinformatics to interpret results of genetic testing and establish a process to manage variants of uncertain significance.
d. Use a standardized reporting format, with the option of providing both a hard and an electronic copy of results to the patient.

4. Return of genetic test results to patients should follow a standardized process, as follows:
   a. First assess overall literacy and understanding and then clarify objectives and expectations before discussing results with the patient.
   b. Tailor disclosure of results to the level of comprehension of the patient.
   c. Gauge patient attitudes towards benefits and threats, consider sociocultural and psychological factors and recognize their intentions for the future.
   d. Communicate in everyday, jargon-free language and provide written and/or pictorial information according to the level of comprehension of the individual.
   e. Restrict reporting of variants in general to those with clear pathogenic or likely pathogenic impact; refrain from reporting results based on benign variants or common polymorphisms.
   f. Variants of uncertain significance may be reported, conditional on communication of the result and its implications to the patient being undertaken by a genetic counsellor, or a clinician with expertise in genetics.
5. Follow-up and re-assessment of genetic test results should involve the following:
   a. Establish a process for patient follow-up regarding questions or concerns that may arise at a later time.
   b. Assess subsequent changes in attitudes, behaviour and adherence to treatment advice of patients.
   c. Carry out regular performance audits to improve the quality of genetic services.
   d. Re-interpret genetic findings regularly, as a collaboration between the issuing laboratory and a clinician with expertise in genetics, accounting for new phenotypic findings in the patient and family and for evolving research knowledge.
6. Diagnostic genetic testing of index cases with suspected FH should be requested by a specialist clinician skilled in counselling, genomic medicine and the care of patients and families with FH. Where indicated (for example, rural centres and remote regions), diagnostic genetic testing of index cases may be requested by a general practitioner guided closely by a specialist clinician.
7. Referral to a professional genetic counselling service should be considered, whenever feasible, to optimize the counselling process for all patients and families at risk of FH.
8. Genetic test results (positive, negative or indeterminant) should be disclosed by an appropriate health-care provider, such as a skilled and experienced clinician, including a family doctor, or certified genetic counsellor.
9. Simple and pragmatic tools for counselling, consenting and disclosure of genetic information should be developed and tested to support health-care professionals in providing genetic testing.
10. Cascade testing of family members should be based on shared decision-making and a fully informed consenting process; results should be communicated in a timely manner, with appropriate risk communication and counselling offered.

11. Cascade testing should ideally be centrally coordinated by a well-resourced, dedicated centre. Cascade testing may be undertaken by a general practitioner with skills in the care of patients and families with FH, under the guidance of an appropriate specialist. The organization of cascade testing may vary according to differences in health policies across and within countries at national, state and regional levels.
12. Direct notification of at-risk relatives regarding their risk of FH should generally be undertaken (or pursued) only with authorization from the proband or index case.
13. Probands and index cases with FH should be offered tools and resources by their health-care providers to assist them in communication about the risk of FH with their relatives.
14. Digital technologies (such as chatbots and social media) should be used, with due consideration to safety and privacy issues, to increase the reach, adoption and effectiveness of family communication about FH and cascade testing of families.
15. Novel family communication tools and programmes (such as technology including secure web portals, chatbots and direct contact by a clinician) should be tested for acceptability, feasibility and effectiveness before implementation.
16. The process of risk notification of at-risk relatives should comply with local legislation and institutional guidelines; risk notification may be indirect (such as providing a family letter for the notifier to share with relatives) or direct (such as the clinical service directly contacting relatives after receiving consent or authorization from the proband or index case).
17. At-risk relatives should be notified directly without authorization from the proband or index case only if there is specific legislative provision for breach of confidentiality; this legislative provision may vary between countries.
18. Cascade testing should ideally be integrated with all strategies for the detection of index cases and be linked to a national registry and biobanking facility.

See Box 2 for core implementation strategies.

Box 2

Genetic testing and counselling for familial hypercholesterolaemia

Core implementation strategies:

- Establish a centre for coordinating cascade testing and a peer-support group
- Use standardized processes for consenting, testing and reporting of results
- Ensure the genetic test requestor is skilled in counselling, genomics and familial hypercholesterolaemia
- Use digital tools and practical resources to facilitate counselling and risk communication
- Align testing processes with local legislation on privacy and data protection
- Use shared decision-making and decision support tools to enable testing
- Integrate with other screening strategies and link to local or national registry

Management

Risk stratification

FH is commonly considered to be a condition associated with a high frequency of ASCVD, but the risk is widely heterogeneous[1,2,16]. The development of ASCVD in FH is driven predominantly by the cumulative burden of LDL-cholesterol concentrations, starting from birth and increasing with age if untreated[1,3,104]. The severity of the genetic defect causing FH determines the progression of ASCVD[90], which is markedly greater in patients with HoFH than in those with HeFH[1,2,18]. However, the progression of ASCVD varies among individuals with a given FH-related gene variant, which relates to behavioural, clinical and other genetic factors[2,80,81,105,106]. Risk stratification can identify patients who require escalation of treatment and guide the best use of health-care resources[2,106,107].

Male sex, delayed initiation of cholesterol-lowering therapy, smoking, low HDL-cholesterol concentration, obesity, diabetes mellitus, hypertension, chronic kidney disease and elevated Lp(a) concentration are all independently predictive of the risk of ASCVD in patients with FH[80,81,108–111]. The prevalence of hypertension and diabetes in patients with FH varies according to the world region and both increase with age[21,112]. Two robust risk-prediction equations, based on a wide spectrum of predictor variables, have been tested prospectively and may have clinical value in adults with HeFH[105,113]. However, further validation of these equations is required in different ancestries and clinical settings[2,106,114,115]. Elevated Lp(a) and LDL-cholesterol concentrations and the presence of hypertension can also accelerate the development and progression of aortic valve disease in patients with FH[116]. Elevated Lp(a) concentrations are also predictive of the presence of polyvascular disease in patients with HeFH[117]. Coexistent illness, such as coronavirus disease 2019 (COVID-19), increases the risk of myocardial infarction in patients with FH[118].

Despite the conventional view that men have a higher incidence of ASCVD than women[21,110,119], registry data suggest a relatively high standardized mortality ratio for coronary artery disease in women with severe FH[120]. Use of statins and attainment of LDL-cholesterol goals are less frequent in women than in men with FH[121,122] and independently relate to ancestry[121]. There is a clear need for improved assessment of sex-specific risk factors for ASCVD, such as reproductive history, in women with FH[123–125]. Improved tools for predicting lifetime risk of ASCVD in children and younger patients with HeFH are also required[2,13,17,126,127]. Polygenic risk scores for hypercholesterolaemia and ASCVD[128–131] may be valuable in predicting the risk of ASCVD in patients with FH[132], subject to resolving analytical, interpretive and risk-communication barriers and the influence of ancestry[132].

Although infrequently encountered in contemporary practice[133], the presence of tendon xanthomas signifies high cumulative exposure to elevated circulating LDL-cholesterol concentrations and may indicate a high risk of ASCVD[2,17,134–137]. However, imaging of coronary and carotid arteries provides the most accurate and direct method to assess ASCVD in patients with FH[2,17,107]. In adults, coronary artery calcification is a good discriminator of the presence of ASCVD[138,139] and increases the predictive value of the SAFEHEART risk equation in genetically defined patients with FH[140]. Use of CT coronary

Table 4 | Clinical recommendations on risk stratification in patients with familial hypercholesterolaemia

Clinical recommendations	Class	Level
1. Routine assessment and stratification of the risk of ASCVD in all patients with FH should be used to develop effective personalized treatment plans and guide overall management, aiming to maximize reduction in the risk of cardiovascular events and improve quality of life	1	B
2. All patients with FH, including children and adolescents, should be assessed for the presence of heart-healthy behaviours and non-cholesterol risk factors (that is, age, sex, smoking, hypertension, diabetes, obesity and mental health conditions) to stratify the risk of ASCVD	1	B
3. The use of coronary artery disease polygenic risk scores may be considered for stratifying the risk of ASCVD in patients with HeFH, but their value in patient care remains to be established	3	B
4. Additional factors particularly relevant to FH that should be assessed to stratify risk include plasma or serum concentrations of LDL-cholesterol and lipoprotein(a) at diagnosis, LDL-cholesterol life-years, family history of premature ASCVD (especially in first-degree relatives), tendon xanthomas (detected clinically or with imaging) and a positive genetic test result if available	1	A
5. Female-specific factors (such as reproductive history, duration off statin therapy owing to pregnancy and breast feeding, and age at menopause) should be considered when assessing the risk of ASCVD in women with FH	2	B
6. Use of FH-specific cardiovascular risk calculators (such as the SAFEHEART risk equation and the FH Risk Score) should be considered to assess the risk of ASCVD in adult patients with an established diagnosis of HeFH	2	B
7. Cardiovascular risk calculators developed for the general population (such as the Framingham Risk Score, Pooled Cohort Equation, SCORE-2 or QRISK-3) should not be used in patients with FH	1	B
8. In asymptomatic adult patients with HeFH, CACS, CT coronary angiography and carotid ultrasonography may be considered to document the presence and extent of atherosclerotic plaque burden and to guide risk assessment, the timing of initial evaluation being dependent on clinical context and indications	3	B
9. Use of FH-specific cardiovascular risk calculators combined with CACS should be considered to risk stratify adult patients with FH treated with statins	2	B
10. In children and adolescents with HeFH, measurement of carotid intima–media thickness with ultrasonography should not be routinely considered for assessing the risk of ASCVD in clinical practice, because extensive technical expertise is required and clinical value is not established	2	B
11. In children and adolescents with HeFH, CACS, CT coronary angiography and current FH risk calculators (such as the SAFEHEART risk equation or FH Risk Score) should not be used to assess ASCVD risk	1	C
12. In all patients with HoFH, CT coronary angiography (or cardiac catheterization), carotid ultrasonography (or more advanced methods), echocardiography and exercise stress testing should be offered, at initial diagnosis and as clinically indicated (for example, because of cardiac symptoms or a high plaque burden at diagnosis), to assess coronary atherosclerosis (particularly high-risk coronary ostial disease), carotid plaques, atheromatous involvement of the aortic valve (or root), aortic stenosis and inducible myocardial ischaemia, respectively, with the aim of guiding overall management, including the intensity of the cholesterol-lowering therapy	1	B

ASCVD, atherosclerotic cardiovascular disease; CACS, coronary artery calcium scoring; FH, familial hypercholesterolaemia; HeFH, heterozygous familial hypercholesterolaemia; HoFH, homozygous familial hypercholesterolaemia.

angiography shows promise[2,17,141–144], but more evidence is required to establish its value for the management of asymptomatic patients with HeFH. No data are available to support the use of coronary imaging at any specific age in adults with HeFH, so the decision is primarily driven by clinical context and indications. However, on the basis of community studies of asymptomatic individuals without FH, cardiac imaging (including coronary artery calcium scoring) may be useful in the assessment of adults with HeFH aged <35 years[144,145]. Carotid ultrasonography, with measurement of intima–media thickness, has been valuable in research studies and is particularly appealing in children[13,41,146]. However, the methodology is not universally standardized, and accurate measurement of intima–media thickness requires considerable technical expertise[107], precluding current routine use in risk assessment. Because of the extremely high risk of ASCVD in patients with HoFH, cardiovascular imaging of coronary arteries, the aortic root and other arterial territories (the aortic arch, descending aorta and carotid, subclavian, renal and ilio-femoral arteries) has a crucial role in risk stratification and management of these patients[18,76,77,147–149]. Limited access to cardiovascular imaging modalities might partly account for the worse cardiovascular prognosis of patients with HoFH from lower-income countries than those from higher-income countries[22].

Recommendations are provided for risk stratification in patients with FH (Table 4).

Implementation recommendations on risk stratification of patients with FH

1. Risk assessment and stratification strategies should be used to triage patients for referral to other services involved in the multidisciplinary care of FH (such as apheresis; general practice support; specialty care in paediatrics, cardiology or diabetes and nicotine cessation programmes).
2. Clear and salient information in written, diagrammatic and electronic format that recognizes cultural, psychological, language and health literacy barriers should be designed and used, together with shared decision-making, to communicate the outcome of risk assessment and stratification, with the aim of developing personalized treatment plans; recognition of patient-reported experience measures and provision of psychosocial and social support are particularly important.
3. Digital health technologies and decision support systems should be used to facilitate all risk assessment strategies (such as the use of FH risk equations or ASCVD imaging) and the corresponding capabilities and capacity of the workforce caring

for patients; telehealth services with adequate facilities should be used to support the risk assessment of patients in rural and remote regions.

4. All registries should include comprehensive, high-quality data on ASCVD risk, including assessments using validated risk equations and cardiovascular imaging, linked to patient outcomes and used to improve the cost–effectiveness of models of care for FH.

Treatment

Substantial evidence from epidemiological data, natural history studies, clinical trials of cholesterol-lowering treatment in primary prevention and basic science studies mandates that patients with FH receive aggressive cholesterol-lowering therapy and lifestyle management from an early age to maximally reduce the cumulative cholesterol burden[3,150,151]. Mendelian randomization data also support that earlier treatment leads to a greater reduction in ASCVD events by lowering lifetime exposure to LDL-cholesterol; the estimated number needed to treat for adolescents with FH to prevent one heart attack is, impressively, two[3,24].

Given the lack of clinical trials, therapeutic goals for LDL-cholesterol concentrations in adults and children with FH are based on a synthesis of diverse evidence, including expert opinion[2,17,74]. The established principle of lower LDL-cholesterol goals in those at higher risk of ASCVD applies. Most patients with HeFH cannot attain very low absolute concentrations of LDL-cholesterol[21,152–155], even when receiving maximal doses of potent statins and ezetimibe, necessitating the addition of proprotein convertase subtilisin/kexin type 9 (PCSK9)-targeted therapy as a third-line approach[156–160]. Treatment inertia also contributes to the inability to achieve LDL-cholesterol goals, emphasizing the need for greater education and support for practitioners[9,21,161,162]. Bempedoic acid may have a role in the management of FH, given evidence of longer-term safety and efficacy, but is approved for use only in adults[163]. Potential toxicity of medications needs careful consideration[164], given that most adult patients with FH will be receiving two or more drugs and are, therefore, at risk of drug–drug interactions; judicious monitoring of clinical and laboratory safety is required. Statin intolerance should be investigated and managed according to the established guidelines[165–169]. Adherence to a healthy lifestyle benefits patients with FH[170], mandating that guidelines specified for the prevention of ASCVD in the general population be followed[10,11,17,40,171]. Comorbidities, such as obesity, diabetes, hypertension, psychological conditions and coronary artery disease[21] should be managed in patients with FH according to the relevant guidelines[10,11,171]. In patients with FH and established clinical ASCVD, the use of aspirin, colchicine and eicosapentaenoic acid should be implemented according to evidence-based guidelines for secondary prevention of ASCVD[172–178].

Primary evidence supporting the treatment of HeFH in children derives from clinical trials of statins, ezetimibe, colesevelam and PCSK9 inhibitors, with end points related to reductions in LDL-cholesterol concentration and to safety. Systematic reviews, registry data and cohort studies have confirmed the efficacy, tolerability and safety of statins for lowering LDL-cholesterol levels (32% mean reduction in LDL-cholesterol concentration in children with HeFH receiving statin therapy between baseline and up to 48 weeks of treatment compared with placebo[179]), with increased efficacy for higher doses of more potent statins[179–186]. Trials of statins as first-line therapy also show improvements in carotid intima–media thickness[146]. The efficacy in lowering LDL-cholesterol concentrations has also been reported for colesevelam (12% mean reduction)[187], ezetimibe (27% mean reduction)[188] and PCSK9 inhibitors (44% mean reduction)[189–191]. A systematic review of unbiased studies showed a small but significant effect of diet in lowering LDL-cholesterol levels[192]. There are new recommendations on how best to change lifestyle-related behaviour to reduce the risk of ASCVD in children[104,193]. Poor adherence to treatment[194], inertia to initiation of treatment among paediatric specialists[195] and other barriers[196] need to be addressed. Genetic testing may increase the use of statins in children[197]. A family history of ASCVD and past personal experiences can influence treatment preferences in adolescents and young adults[198].

A landmark study of patients with HeFH and statin therapy beginning in youth, with follow up to age 40 years, showed substantially lower rates of ASCVD and death compared with their affected parents (1% versus 26% for ASCVD; 0% versus 7% for mortality); the achieved mean LDL-cholesterol concentration was 4.16 mmol/l (161 mg/dl), and the long-term safety of treatment was confirmed[41]. Carotid intima–media thickness in those treated with statins was similar to that in unaffected siblings, with evidence of a dose–response effect[41]. Longer-term observational studies (over 3–9 years), combined with clinical experience, also suggest minimal adverse effects of statins, without evidence of muscle injury, liver dysfunction or incident diabetes[181–186].

Severe FH, particularly HoFH, remains difficult to treat[18,22]. As a result of markedly elevated LDL-cholesterol concentrations from conception, patients with severe FH have marked acceleration of ASCVD and aortic stenosis, impairing quality of life[199,200] and leading to premature death[18,22,201–205]. The past three decades have seen major advances in treatment[104,157,160,206] that have led to improvements in ASCVD outcomes[205]. The early use of combination cholesterol-lowering therapies, including high-intensity statins, ezetimibe and PCSK9-directed therapies (which act mainly by augmenting LDL receptor (LDLR) function), forms the mainstay of treatment for HoFH[18,156,207–211], but the response is dependent on residual LDLR function. The use of probucol has been promoted in Japan to lower LDL-cholesterol concentrations in patients with HoFH[212]. With the availability of therapies that work independently of LDLR function, such as lomitapide (which inhibits microsomal triglyceride transfer protein) and angiopoietin-like protein 3 (ANGPTL3) inhibitors[18,157,213–215], lower therapeutic goals for LDL-cholesterol are now achievable. Clinical trials confirm the efficacy of ANGPTL3 inhibitors in patients with HoFH[214], including children[216]. PCSK9 inhibitors are effective in patients with residual LDLR function, but longer-term safety data are required[157]. Evinacumab (an ANGPTL3 monoclonal antibody) has fewer adverse effects than lomitapide, but its long-term efficacy and safety remain to be confirmed[214,215]. Lipoprotein apheresis is effective in treating HoFH[217–223] (see specific section discussed subsequently). The use of lipoprotein apheresis in patients with HoFH before, after or in combination with the new LDLR-independent therapies will depend on availability, expertise, costs and patient preference[18]. Lipoprotein apheresis should, for example, be first used in countries without access to the new therapies. Emerging therapies for HoFH include liver-directed gene transfer of *LDLR* and CRISPR-based gene editing directed at *ANGPTL3* or *PCSK9* (refs. 221,224,225). Preliminary studies indicate their potential therapeutic value, but clinical trials of safety and efficacy are required.

Liver transplantation may be offered as a therapeutic option in the context of shared decision-making, particularly in young patients with severe HoFH (caused by biallelic null variants) who are refractory to current therapies and in whom the use of lipoprotein apheresis is not feasible[18,104,221,226,227]. Liver transplantation can lead to sustained normalization of LDL-cholesterol concentrations[228–230] and lowering of Lp(a) concentrations. Regression of coronary atherosclerosis has

been reported[231,232], but effects on aortic stenosis are less clear[230,231]. Combined liver and heart transplantations from a common donor should be considered in patients with poor cardiac prognosis[233]. The benefits and risks of liver transplantation in patients with HoFH need to be carefully considered[18,221,226,228–234].

The use of cardiovascular imaging modalities has been advocated for risk stratification and for monitoring of ASCVD during treatment of patients with FH[13,16–18,76,77,80,147,202,235,236]. CT coronary angiography has potential clinical utility because it integrates the effect of LDL-cholesterol burden on ASCVD and can guide therapy, improve patient adherence and assist in prioritizing cardiac investigations (such as invasive coronary angiography and exercise stress testing) in adult patients with HeFH[2,17]. However, the precise clinical and economical value of this approach remains to be demonstrated. As clinical ASCVD and aortic stenosis are common in patients with HoFH, the use of imaging is integral to management protocols[17,18,104,107] for escalating LDL-cholesterol-lowering and other medical treatments and for considering cardiac interventions, such as aortic valve (or root) and coronary artery bypass graft surgery.

In summary, earlier initiation of treatment, improved adherence to medications, cost minimization and better access to novel therapies are needed to maximize health outcomes for patients with FH. Treatment of FH should fundamentally be patient-centred and underpinned by the core principles of shared decision-making across the continuum of care[2,17,198,237–240]. Recommendations are provided for the treatment of adults with HeFH (Table 5 and Fig. 2), children with HeFH (Table 6 and Fig. 2) and patients with HoFH (Table 7 and Fig. 3).

Implementation recommendations on the treatment of patients with FH

1. A personalized treatment plan should be developed for all patients using shared decision-making, considering age, additional risk factors for ASCVD, psychological and sociocultural factors, economic status, barriers to adherence, and personal and family values and preferences.
2. Clear and salient information (in written, diagrammatic and electronic format) that addresses age-related, sociocultural, psychological, language and health literacy barriers should be designed and used to develop personalized treatment plans.
3. Personalized treatment plans for children and adolescents should be designed on the basis of shared decision-making with parents and, in the case of adolescents, using a developmentally appropriate approach.
4. Care pathways should be clearly defined between general practice and paediatric centres: well-controlled and lower-complexity patients should be managed in general practice; less well-controlled (such as those who are not achieving LDL-cholesterol goals or who have several cardiovascular risk factors) and higher-complexity patients (such as those with HoFH) should be managed in specialist centres, with the option of shared care with general practice.
5. Children and adolescents with HoFH should ideally be managed by a multidisciplinary team in centres with paediatric expertise in lipidology, cardiology and apheresis.
6. Management of children and adolescents should ideally focus on the nuclear or immediate family, with (at a minimum) annual reviews in general practice and/or paediatric services to assess well-being, mental health issues, the safety of medication and adherence to therapy.
7. Transition of care of adolescents to adult services should be planned well in advance, and support should be given to facilitate and sustain self-management and involvement in shared management into adulthood.
8. Before prescribing medication and other interventions in children or adolescents with FH, clinicians should engage in a patient-centred and family-centred discussion that uses shared decision-making and covers risk stratification, expected ASCVD risk-reduction benefit, potential adverse effects and drug interactions, sociocultural and economic factors, and values and preferences. At subsequent reviews, clinicians should use, as clinically indicated, a behavioural counselling approach (such as the 5A model of assess, advise, agree, assist and arrange) to address and promote adherence to medication and other treatments.
9. Multifactorial barriers (for example, those related to patients, clinicians, drugs, health-care systems and sociocultural, psychological and financial circumstances) to medication adherence in adult patients with FH should be systematically identified and addressed using appropriate resources by all health service providers; this approach should extend beyond medical care to include a more holistic approach for meeting the emotional, psychological and self-management needs of patients.
10. Clinicians, health systems and health-care plans should identify patients who are not receiving guideline-directed medical therapy and facilitate the initiation of corresponding treatment using multifaceted strategies.
11. Multiple interventions for improving adherence to medication should be used, with appropriate resources, for managing patients with FH; these interventions should include provision of free or subsidized medication, thereby ensuring affordability of established drugs and special access to new drugs; telephone, mobile text, e-mail and calendar reminders; use of single-pill combination drug therapies; expanded role of allied health-care provider interventions, such as simplified dosing by pharmacists and motivational counselling by skilled nurses and pharmacists, and comprehensive multidisciplinary education programmes; patient tools for improving knowledge and understanding of medication and self-care; decision support aids to empower patients and improve the patient–provider relationship; clinical decision support system-based interventions to improve the quality and safety of prescribing; and financial incentives and rewards for treatment goals attained. These strategies should be used in addition to adaptive, complex interventions shown to be effective in the care of other chronic conditions.
12. Iterative strategies, based on key performance indicators (such as adherence to treatment guidelines, attainment of therapeutic goals and patient-reported outcomes and experience measures, notably quality of life in patients with HoFH), should be used regularly or as clinically indicated. These approaches should ideally be part of an audit cycle every 12 months and aim to improve the reach, effectiveness, adoption, implementation and sustainability of service delivery. Multifaceted strategies should be used to improve implementation of treatments.
13. Services for FH should host regular multidisciplinary case discussions, provide local guidance on the best standards of treatment and develop strategies for implementing these recommendations.

Table 5 | Clinical recommendations on the treatment of adults with heterozygous familial hypercholesterolaemia

Clinical recommendations	Class	Level
1. All patients should be offered advice on cardiovascular risk factors (including smoking, hypertension, obesity, metabolic syndrome and diabetes mellitus) and counselled on lifestyle modifications (a fat-modified, heart-healthy diet, regular physical exercise, reduction in psychological stress, moderation in alcohol intake and sleep hygiene)	1	B
2. In patients whose treatment is stable, non-fasting lipid profiles should be used to monitor treatment, but when making decisions on changing treatment, a fasting LDL-cholesterol concentration should be used, especially in patients with concomitant hypertriglyceridaemia	1	B
3. After approximately 50% reduction in LDL-cholesterol concentration, the following treatment goals should be considered according to the level of ASCVD risk: (a) LDL-cholesterol concentration <2.5 mmol/l (<100 mg/dl) in the absence of ASCVD or other major ASCVD risk factors; (b) LDL-cholesterol concentration <1.8 mmol/l (<70 mg/dl) with imaging evidence of ASCVD alone or other major ASCVD risk factors and (c) LDL-cholesterol concentration <1.4 mmol/l (<55 mg/dl) with clinical ASCVD	2	B
4. In patients with a recurrent ASCVD event within 2 years while taking maximally tolerated statin treatment, a lower LDL-cholesterol goal of <1.0 mmol/l (<40 mg/dl) may be considered	3	C
5. Use of secondary treatment goals based on non-HDL-cholesterol and apolipoprotein B levels may be considered, particularly in patients with hypertriglyceridaemia	3	C
6. Maximally tolerated high-potency statins (such as atorvastatin, rosuvastatin or pitavastatin) with or without ezetimibe and/or bempedoic acid (if available), and a fat-modified, heart-healthy diet should initially be used in most patients (for exception, see recommendation 9 below) to achieve LDL-cholesterol goals	1	A
7. If LDL-cholesterol goals are not achieved, plant sterols (stanols) or bile acid sequestrants (such as colesevelam) may be considered as adjunctive therapies	3	B
8. PCSK9-targeted therapy (monoclonal antibodies or a small interfering RNA (inclisiran)) should be added if LDL-cholesterol goals are not achieved with diet, maximally tolerated statins, ezetimibe, bempedoic acid and other adjunctive therapies	1	A
9. In patients with extremely high-risk HeFH (for example, after myocardial infarction or those with multivessel coronary atherosclerosis or polyvascular disease), the combination of a high-potency statin, ezetimibe and PCSK9-targeted therapy should be considered as first-line treatment	2	B
10. Plasma levels of hepatic aminotransferases, creatine kinase, glucose and creatinine should be measured before starting drug therapy. Plasma levels of hepatic aminotransferases should be monitored in patients taking statins (particularly with an increased risk of hepatoxicity related to a history of liver disease, excess alcohol or adverse drug interactions), and plasma levels of creatine kinase should be measured if musculoskeletal symptoms are reported; plasma levels of glucose or HbA1c should be monitored if there are risk factors for diabetes	1	B
11. Provided there are no bleeding contraindications, low-dose aspirin may be considered as a primary prevention measure in asymptomatic patients at higher risk of ASCVD (those with a marked elevation of lipoprotein(a) concentration, diabetes or adverse findings on cardiovascular imaging)	3	C
12. Cholesterol-lowering drug therapies and other anti-ASCVD treatments should be continued and optimized during acute illness (such as respiratory infections, including COVID-19), unless their use is specifically contraindicated, as with potential adverse drug interactions and abnormal liver function	1	B
13. Patients with cardiovascular sequelae of COVID-19 should be investigated, assessed and managed according to contemporary expert guidelines	1	B
14. All adult patients, especially those with ASCVD, aged >65 years or at an increased risk of exposure, should be offered SARS-CoV-2, influenza, pneumococcal and other related vaccines as a preventive measure against respiratory infections and acute ASCVD events, in accordance with country-specific health policy	1	C
15. Although CACS is useful in the initial risk assessment in asymptomatic patients before starting cholesterol-lowering medication, CACS should not be used to monitor the effectiveness of cholesterol-lowering treatment	1	B
16. In asymptomatic patients, imaging of ASCVD (for example, carotid ultrasonography and CT coronary angiography for the detection of plaques and stenoses) may be considered for monitoring the effectiveness of cholesterol-lowering treatment	3	B

See Fig. 2 for a simplified treatment algorithm for heterozygous FH. ASCVD, atherosclerotic cardiovascular disease; CACS, coronary artery calcium scoring; COVID-19, coronavirus disease 2019; FH, familial hypercholesterolaemia; HeFH, heterozygous familial hypercholesterolaemia; PCSK9, proprotein convertase subtilisin/kexin type 9; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

14. Paediatric and adult services for FH should participate in a national and international network of FH clinical centres to share educational, clinical and research experience and develop a comprehensive and high-quality registry of patients. Real-world registry data from these collaborations should be regularly used to assess the safety and effectiveness of conventional and new drug therapies, to advocate for policy change to close treatment gaps, to educate registrants and health-care providers and to provide a resource of potential participants for clinical trials of new interventions.
15. Multidisciplinary preoperative and postoperative care, with shared decision-making (involving patients and close relatives), should be prioritized in all management plans for patients with severe HoFH undergoing liver transplantation; as a fundamental principle of quality health care, this radical treatment should be undertaken only in highly experienced paediatric or adult liver transplantation centres.
16. The long-term cardiovascular and lipid outcomes and the complications of liver transplantation, as well as patient-reported outcome measures (including mental health issues), should be audited

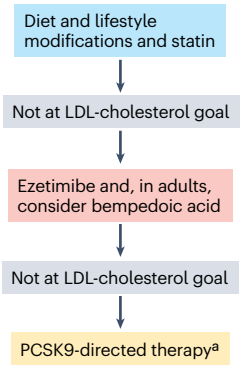

Fig. 2 | Treatment algorithm for patients with heterozygous familial hypercholesterolaemia. PCSK9, proprotein convertase subtilisin/kexin type 9. [a]May be considered in children and adolescents with additional risk factors for atherosclerotic cardiovascular disease, noting limited long-term safety data.

regularly and recorded in a dedicated registry, and this should be used to promote the best standard of care across all centres.

17. The principles underpinning the concept of rare genetic (or intractable) diseases should be used to seek government funding for comprehensive care of all patients with HoFH, which may include developing a dedicated, specialist centre, as well as special access schemes for new therapies for all patients with HoFH.

See Box 3 for core implementation strategies and Fig. 4 for a summary of recommendations for addressing barriers to adherence.

Pregnancy

Fertility rates are unchanged in women with FH. Safe, effective and acceptable methods of contraception are, therefore, of utmost importance in avoiding unplanned pregnancies, especially in women with HoFH[18,241]. Family planning should be addressed early in both women and men and should involve LDL-cholesterol testing of the partner and counselling; pre-conception counselling and prenatal and pre-implantation genetic testing with counselling of couples known to have FH is particularly important. Pregnancy and lactation in women with FH results in a prolonged exposure to elevated LDL-cholesterol concentrations owing to both the discontinuation of cholesterol-lowering therapy and the physiological changes associated with pregnancy itself[242–244]. This exposure may have effects on the cardiovascular outcomes of mothers and their progeny[123,245].

Women with FH should have pre-conception counselling about the risks of pregnancy and have their level of ASCVD risk evaluated, with a full cardiovascular assessment, if clinically indicated[246,247]. Lifestyle and non-cholesterol risk factors should be optimized, and management options including contraception up to and during pregnancy and lactation should be discussed[243,248,249]. An individualized approach depending on the severity of the disease, extent of hypercholesterolaemia and the presence or absence of ASCVD should be adopted, weighing the risks and benefits of therapies[246,250]. Cumulative loss of years on statin treatment during pregnancy and breastfeeding may have a bearing on ASCVD outcomes in women with FH[123]; early detection and treatment of FH and judicious family planning advice will minimize this potential risk. Children born to a parent with HoFH and a parent without FH are obligate heterozygotes and should be formally diagnosed and offered treatment by the age of 8 years[13,14,17].

Table 6 | Clinical recommendations on the treatment of children with heterozygous familial hypercholesterolaemia

Clinical recommendations	Class	Level
1. At diagnosis, all patients should be offered counselling on following a heart-healthy, low saturated fat (<10% of total calories), high-fibre diet and correcting all other behavioural risk factors for ASCVD, particularly smoking, lack of exercise, obesity and psychological stress	1	B
2. Pharmacological treatment should be offered at age 8–10 years with an LDL-cholesterol concentration >4.9 mmol/l (>190 mg/dl), recorded on two occasions with a fasting lipid profile	1	B
3. Pharmacological treatment should be considered for those aged 8–10 years with an LDL-cholesterol concentration >4.0 mmol/l (>160 mg/dl), recorded on two occasions with a fasting lipid profile, in the presence of multiple ASCVD risk factors or family history of premature ASCVD	2	B
4. Initiation of pharmacological treatment at age <8 years may also be considered with an LDL-cholesterol concentration >4.9 mmol/l (>190 mg/dl), recorded on two occasions	3	B
5. An LDL-cholesterol goal of <3.5 mmol/l (<135 mg/dl) or approximately 50% reduction may be considered in patients with no additional risk factors for ASCVD (for example, diabetes, hypertension, elevated lipoprotein(a) concentration or parental history of ASCVD in the second or third decade of life); non-fasting blood samples may be used to monitor LDL-cholesterol levels in those receiving stable therapy	3	C
6. An LDL-cholesterol goal of <2.5 mmol/l (<100 mg/dl) may be considered in patients with additional risk factors for ASCVD	3	C
7. To achieve LDL-cholesterol treatment goals, the initial medication of choice should be a statin that is approved in the relevant country (or jurisdiction) for use in paediatric patients	1	A
8. Other medications that should be considered, in addition to the maximal tolerated and safe dose of a statin, are ezetimibe and bile acid sequestrants	2	B
9. Use of a PCSK9 inhibitor may be considered according to clinical indications and regulatory approvals, with the caveat of limited evidence of long-term safety in children and adolescents	3	B
10. Plasma levels of liver enzymes, creatine kinase, glucose and creatinine should be measured before starting statin therapy; plasma levels of liver and muscle enzymes and glucose should be monitored as in adults	1	B
11. Growth and adherence to lifestyle management and LDL-cholesterol-lowering medication should be monitored annually or as clinically indicated	1	A
12. Adolescent girls should be offered advice on the basis of current recommendations regarding contraception and the use of lipid-lowering medications in pregnancy	1	B

See Fig. 2 for a simplified treatment algorithm for heterozygous familial hypercholesterolaemia. ASCVD, atherosclerotic cardiovascular disease; PCSK9, proprotein convertase subtilisin/kexin type 9.

Table 7 | Clinical recommendations on the treatment of patients with homozygous familial hypercholesterolaemia

Clinical recommendations	Class	Level
1. Treatment of patients with HoFH should begin at diagnosis and ideally by the age of 2 years, with counselling on heart-healthy lifestyles, psychological support for the family and LDL-cholesterol-lowering medications	1	B
2. The following treatment goals should be considered: (a) LDL-cholesterol concentration <2.5 mmol/l (<100 mg/dl) in the absence of ASCVD or other major risk factors for ASCVD; (b) LDL-cholesterol concentration <1.8 mmol/l (<70 mg/dl) with imaging evidence of ASCVD alone or additional major risk factors for ASCVD; (c) LDL-cholesterol concentration <1.4 mmol/l (<55 mg/dl) with a previous ASCVD event; fasting and non-fasting blood measurements of LDL-cholesterol concentrations could be used as recommended for patients with HeFH	2	B
3. To achieve LDL-cholesterol goals, all currently approved medications (such as high-potency statin, ezetimibe and colesevelam) should be used; medications should be used sequentially, starting with a statin with rapid up-titration to maximally tolerated and approved doses, followed within 8 weeks by the addition of ezetimibe and possibly colesevelam if tolerated	1	B
4. A PCSK9 inhibitor should be added within a further 8 weeks in patients without biallelic *LDLR* null mutations and continued only after demonstration of an acceptable response (≥15% additional reduction in LDL-cholesterol concentration)	1	B
5. In the highest-risk patients (for example, those with symptomatic ASCVD or multivessel coronary atherosclerosis), the combination of a high-potency statin, ezetimibe and PCSK9-targeted therapy should be strongly considered as first-line treatment	2	B
6. Lipoprotein apheresis should be offered, if feasible, at the age of 3 years (and no later than 8 years) when LDL-cholesterol goals are not achieved with a maximally tolerated regimen of cholesterol-lowering medications	1	A
7. In patients with markedly elevated LDL-cholesterol concentrations when receiving conventional therapy or with rapidly progressive ASCVD, the use of lomitapide (a microsomal triglyceride transfer protein inhibitor) or evinacumab (an angiopoietin-related protein 3 inhibitor) should be considered, adjunctive to diet and conventional drugs, to lower the LDL-cholesterol concentration further, especially if lipoprotein apheresis is not available or feasible	2	B
8. In patients with rapidly progressive ASCVD, the use of evinacumab may be considered, adjunctive to diet, conventional cholesterol-lowering drugs and lomitapide, to lower the LDL-cholesterol concentration further, especially if lipoprotein apheresis is not available or feasible	3	C
9. CT coronary angiography, carotid ultrasonography, echocardiography (including measurement of aortic valve gradients) and exercise stress testing should be used, as clinically indicated, to assess the severity and progression of ASCVD, aortic valve (or root) atheromatous involvement and inducible myocardial ischaemia, as well as to guide overall management and the intensity of LDL-cholesterol lowering treatment	1	B
10. Recommendations made above (Tables 5 and 6) for the management of HeFH should be followed concerning control of behavioural and non-cholesterol cardiovascular risk factors, blood sampling to monitor cholesterol-lowering therapy, use of aspirin, treatment of FH during acute illness, use of vaccinations (including for SARS-CoV-2), treatment of cardiovascular sequelae of COVID-19, blood testing protocol for monitoring drug safety and potential toxicities, assessment of growth in children and pre-pregnancy counselling of adolescent girls	1	*
11. Liver transplantation should be considered in patients with HoFH and rapidly progressive ASCVD who do not attain guideline-recommended LDL-cholesterol goals when receiving all available treatment, including lipoprotein apheresis (or who cannot tolerate lipoprotein apheresis or do not have access to suitable lipoprotein apheresis services), and are considered psychologically suitable for this treatment; combined liver and heart transplantation from a single donor should also be considered in the most severely affected patients	2	B
12. Liver transplantation may be considered in patients with HoFH and minimal or stable ASCVD who do not attain an LDL-cholesterol goal of <10 mmol/l (<400 mg/dl) when receiving all available LDL-cholesterol-lowering treatments; this situation will typically apply to children and young adults with severe biallelic null variants in *LDLR*	3	C

See Fig. 3 for a simplified treatment algorithm for homozygous familial hypercholesterolaemia (FH). ASCVD, atherosclerotic cardiovascular disease; COVID-19, coronavirus disease 2019; HeFH, heterozygous familial hypercholesterolaemia; HoFH, homozygous familial hypercholesterolaemia; LDLR, LDL receptor; PCSK9, proprotein convertase subtilisin/kexin type 9; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. *See Tables 5 and 6 for levels of evidence for patients with HeFH pertaining to each of the items listed in recommendation 10.

The need for specific guidelines on the management of dyslipidaemia in pregnancy has been emphasized[251]. First-generation bile acid sequestrants have been used in pregnancy and are not associated with an increased risk of congenital abnormalities[251], but are poorly tolerated[252]. Colesevelam, a more selective bile acid sequestrant, is the best-tolerated agent, but experience in pregnancy is limited. Women with HoFH at high risk of ASCVD, or with established ASCVD or aortic valve disease, should be offered weekly or fortnightly lipoprotein apheresis, if available, during pregnancy[253,254]. The risks and benefits of statin and other lipid-lowering therapies during pregnancy should be discussed[160,251], and the continued use of statin therapy, or the introduction of statin and other lipid-lowering therapies during the second and third trimesters, considered carefully[123,160,241,254–263]. No safety data are available on the use of bempedoic acid, PCSK9 monoclonal antibodies, inclisiran, lomitapide or evinacumab in patients with FH during pregnancy[160]. The FDA has acknowledged the net benefits of statins during pregnancy in women at very high risk of ASCVD[264,265], such as those with HoFH.

Recommendations are provided for the treatment of FH during pregnancy (Table 8).

Implementation recommendations on the treatment of FH during pregnancy

1. The care of pregnant women with FH should be designed to meet the needs of local, regional and remote communities; services should be multidisciplinary, involve the general practitioner of the patient, and ideally be coordinated by a clinician with expertise in FH and obstetric medicine.
2. All women with FH who are planning a pregnancy should ideally be referred for further advice to a specialist centre that provides a dedicated multidisciplinary service and holistic care. Such a service should include care of medical conditions (such as depression, hypertension and gestational diabetes) and counselling (such as psychological and mental health issues) and take account of sociocultural background and preferences and values of patients.

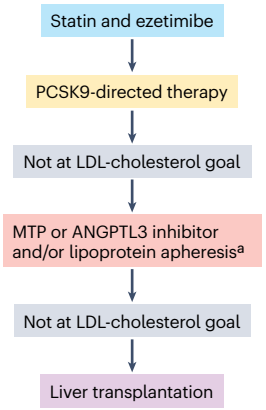

Fig. 3 | Treatment algorithm for patients with homozygous familial hypercholesterolaemia. ANGPTL3, angiopoietin-related protein 3; MTP, microsomal triglyceride transfer protein; PCSK9, proprotein convertase subtilisin/kexin type 9. [a]Depending on availability, preference, expertise and cost.

3. Clear and relevant information (in written, diagrammatic, pictorial and electronic formats) that addresses sociocultural, language and health literacy barriers should be designed and offered to women during pregnancy-related counselling sessions. This information should include shared decision-making, choice of contraception, importance of heart-healthy behaviours, risks of pregnancy, drug safety and teratogenicity, risk of ASCVD from cessation of drug therapy, and care during lactation.
4. Iterative strategies should be used, based on key performance clinical indicators, such as maternal-reported outcome and experience measures, fetal outcomes and quality of life of patients to improve the implementation of care.
5. Existing clinical resources (such as obstetric and gynaecological medicine, lipidology, dietetics, nursing, mental health care, family planning, genetic counselling, imaging facilities, cardiology and diabetes services) should be adapted to provide an integrated model of care for women with FH planning and undergoing pregnancy[241,251,266,267].
6. A clinical quality registry of pregnant women with FH, linked to patient-reported and experience measures, should be used to improve pregnancy and family care.

Lipoprotein apheresis and related pharmacotherapies

Extracorporeal removal of cholesterol-carrying lipoproteins to treat hyperlipidaemia initially involved plasma exchange. This approach was subsequently replaced by lipoprotein apheresis using adsorption, differential filtration or precipitation to selectively remove the apolipoprotein B-containing lipoproteins — LDL and Lp(a) — from plasma or whole blood[217]. Lipoprotein apheresis is a safe and effective means of treating patients with HoFH on a lifelong basis, especially in combination with statins and ezetimibe. Treating 1.5–2.0 times the blood or plasma volumes weekly plus optimal cholesterol-lowering drug therapy reduces interval mean values of LDL-cholesterol by 64–77%[218–220]. Retrospective surveys of patients with HoFH have shown that the lower the LDL-cholesterol concentration when receiving lipoprotein apheresis combined with drug treatment, the greater the reduction in mortality[203,204]. Effectively lowering LDL-cholesterol concentrations with lipoprotein apheresis has also been associated with a reduction in supravalvular aortic stenosis[148] and regression of tendon xanthomas[221,222]. Despite its therapeutic value, for logistical and economic reasons, lipoprotein apheresis is not universally available or used[18,22].

Lipoprotein apheresis robustly reduces elevated concentrations of both Lp(a) and LDL-cholesterol, unlike all currently available cholesterol-lowering drugs, and is a safe means of treating children aged <12 years and pregnant women with HoFH[77,254]. However, its use in other forms of severe hyperlipidaemia, such as statin-refractory HeFH, is diminishing because of the efficacy of PCSK9 inhibitors[223,268]. The future use of lipoprotein apheresis in patients with HoFH may also decrease because of the effectiveness of lomitapide[215,269,270] and the ANGPTL3 inhibitor evinacumab[214]. However, lipoprotein apheresis will continue to be the last resort in patients ineligible for, refractory to or intolerant of cholesterol-lowering drugs[271]; lipoprotein apheresis might also be the best option in countries without access to newer pharmacotherapies[221]. Liver transplantation was referred to earlier as a last resort for patients with HoFH who cannot tolerate lipoprotein apheresis and are refractory to all other therapies[221,230,272]. More studies addressing the experiences and health-related quality of life of patients with HoFH receiving lipoprotein apheresis are needed[199,273]. The following recommendations (Table 9) are updated from existing guidelines on the role of lipoprotein apheresis and novel cholesterol-lowering drugs in managing patients with FH or raised Lp(a) concentrations[15,16,18,69,77,80,202,274,275].

Implementation recommendations on the treatment of FH by lipoprotein apheresis

1. All patients being considered for lipoprotein apheresis should be assessed for physical and psychological suitability for treatment by a specialist with training in lipidology and experience in apheresis, supported by other specialists where indicated.

Box 3

Treatment of familial hypercholesterolaemia

Core implementation strategies:

- Use risk-reduction strategies to triage patients and use cost-effective therapies and resources
- Establish networks of clinical centres to share experience and education; upskill all health-care providers
- Use iterative strategies and key performance indicators to optimize risk-reduction pathways
- Define multidisciplinary care pathways, transitional services for adolescents and dedicated services for family planning and women during pregnancy
- Develop personalized treatment plans using shared decision-making, with culturally appropriate clear information
- Identify patients not receiving guideline-directed therapy and facilitate treatment using multifaceted strategies; use advocacy and peer support
- Use multiple and evidence-informed interventions to improve adherence to medication

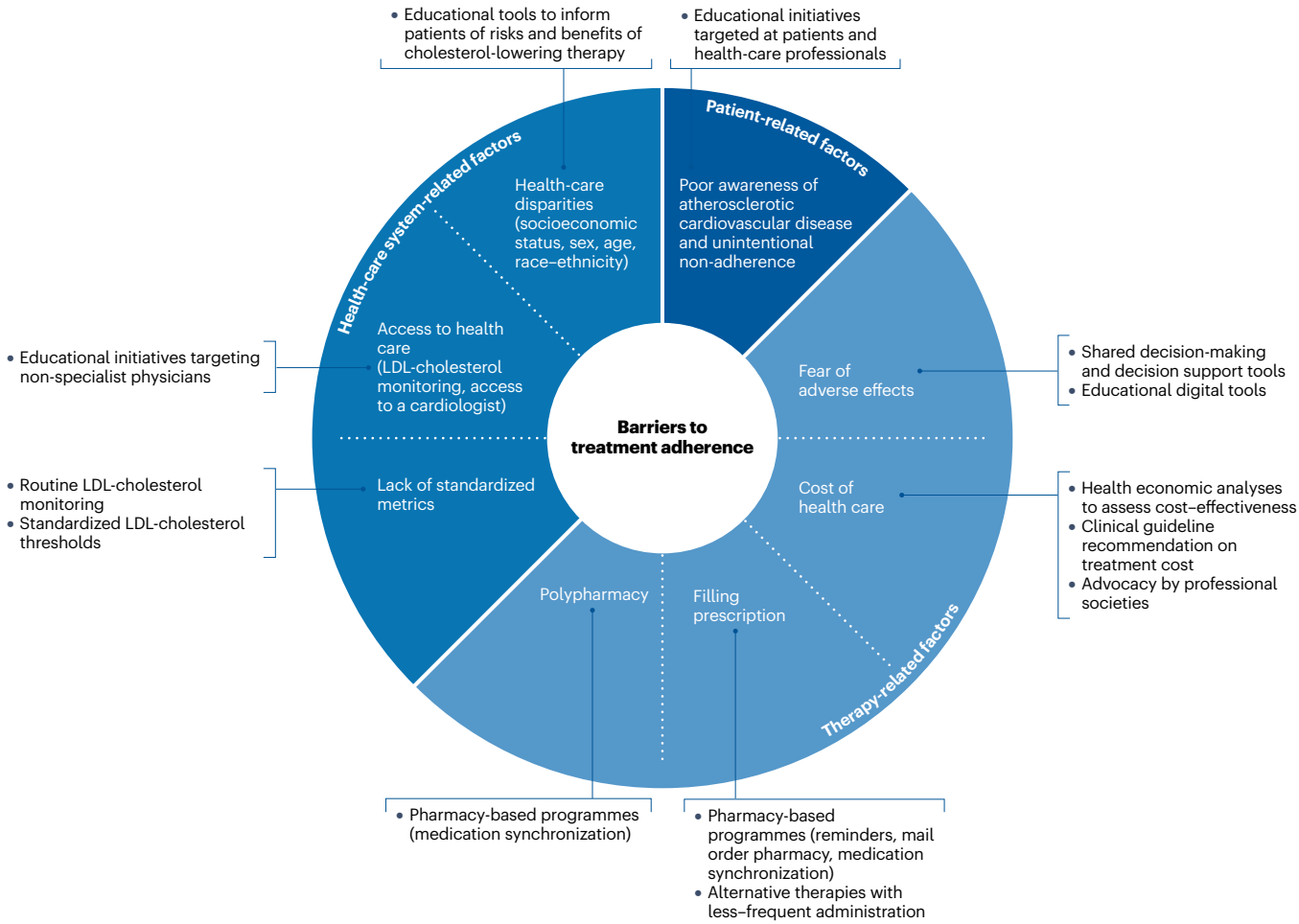

Fig. 4 | Barriers to treatment adherence and suggested solutions. Factors related to patients, therapy and health-care systems that can be barriers to treatment adherence and potential solutions to overcome these barriers. Adapted with permission from ref. 291, Wiley.

2. If lipoprotein apheresis is not available or feasible (for example, because of a lack of resources or in children with HoFH who have a small blood volume), the use of therapeutic plasma exchange (which is more widely available) should be considered as an alternative.
3. Facilities and resources for apheresis services should be regularly reviewed and cost analyses submitted to the relevant organization to obtain adequate financial support for the service.
4. Apheresis services should be designed to meet local needs and be centralized in a dedicated unit, headed by a director who should be the lead of a multidisciplinary team of accredited personnel.
5. Existing clinical infrastructure (for example, haemodialysis, transfusion medicine and vascular surgery services) should be adapted to improve the availability of lipoprotein apheresis and to increase the quality of the service.
6. Given the varied expertise required to provide a quality apheresis service, a coalition of specialties (including lipidology, cardiology, vascular surgery, paediatrics, mental health care, nephrology, transfusion medicine, pharmacy and nursing) should be established; this coalition should hold regular multidisciplinary case meetings, plan implementation strategies for improving service delivery and develop local guidance on the best evidence-based standard of care.
7. Key performance indicators, such as the efficacy, tolerability and safety of lipoprotein apheresis, as well as the effect on patient-reported outcomes and experiences (including quality of life) should be reviewed as clinically indicated and as part of a regular audit cycle every 12 months.
8. Apheresis units should participate in a national or international network of similar centres to share educational, clinical and research experience and to establish and consolidate a comprehensive clinical quality registry of patients receiving treatment.

See Box 4 for core implementation strategies.

General strategies for the implementation of care

Despite the development of several international and country-specific guidelines for the care of FH, substantial gaps remain in their implementation into practice[23,28]. Accordingly, <10% of the estimated

35 million people with FH worldwide have been diagnosed, with <1% of cases identified in most countries[201]. Furthermore, many patients with FH receiving treatment are not attaining LDL-cholesterol goals, with substantial gaps in the care of those with severe FH or HoFH. Major knowledge gaps among patients, clinicians and health-care systems further hinder implementation[29,276,277]. Action is required to alter processes, structures and health-care teams to improve the organization and delivery of care[52,278]. Implementation evidence is essential to effectively manage the changes in health care[29,32].

Design and assessment of implementation recommendations

The use of implementation science to improve clinical practice guidelines has been reviewed previously[29,279]. A five-step process should be followed[29]:

1. Define the evidence-based practice or intervention.
2. Choose an implementation theory, model or framework.
3. Assess determinants, barriers, enablers and context in respect of the practice or intervention.
4. Select implementation strategies.
5. Select options for assessing the outcomes of implementation.

Implementation science entails the design of processes, termed 'implementation strategies', to overcome barriers to and leverage enablers of improved care[280,281]. Implementation science is fundamentally an operational tool to change practice on the basis of the best evidence-informed guidance (step 1), such as clinical practice recommendations provided in this guidance article. Informed by an appropriate implementation model (step 2) and knowledge of barriers and enablers (step 3), implementation strategies can be used to implement clinical guidelines. We have used the ERIC taxonomy[37] (Supplementary Material 1 Appendix 5) to develop general and specific implementation recommendations in this guidance (step 4).

The development of new guidance on FH provides an opportunity to identify potential strategies that could be used to implement recommendations into policy and practice and research their effect on patient outcomes[32,282]. Researching implementation requires the selection of processes for monitoring and evaluating implementation strategies (step 5)[29]. The value of tailored implementation strategies for improving the care of patients with FH is well supported by several studies[58,101,283–286].

A pathway for the iterative development and implementation of cardiovascular guidelines to improve their translation into practice has been recommended[32]. This guidance article on FH proposes both clinical and implementation recommendations to enable translation into policy and practice[29,32]. Local implementation requires an initial assessment of barriers to and facilitators of change, paired with the tailoring of strategies to implement a change in practice[32]. Similar to clinical quality improvement, successful implementation practice relies on monitoring, evaluation and ongoing efforts to ensure the sustainability of changes[287]. This cyclical and iterative process builds new evidence for the implementation of future clinical practice recommendations. The success of implementation in addressing gaps in clinical practice relies on implementing behavioural change at multiple levels of the adaptive health-care system[2,32,288].

General implementation recommendations

1. The design and implementation of health services for FH should deliver quality care that is patient-centred, safe, effective, efficient, equitable, well led and integrated, and sustainably resourced.
2. Care and support processes for FH should be widely based on evidence from public health and prevention and precision

Table 8 | Clinical recommendations on the treatment of familial hypercholesterolaemia during pregnancy

Clinical recommendations	Class	Level
1. All women with FH who are of child-bearing age, including adolescents, should be educated about the risks of pregnancy; advice on safer and preferred methods of contraception, with minimal cardiovascular risk, and the importance of contraception should be reinforced to prevent unplanned pregnancy	1	B
2. Reinforcement and optimization of heart-healthy behaviours, including diet, physical activity and psychological well-being, should be prioritized before, during and after pregnancy and breastfeeding	1	B
3. Pre-pregnancy counselling should be offered to all women before starting a statin, ezetimibe, PCSK9 inhibitor or other lipid-modifying therapies, and this advice should be reinforced as clinically indicated	1	B
4. Assessment of ASCVD using imaging (for example, CT angiography for coronary artery disease or echocardiography for aortic stenosis) should be offered to women with HoFH or high-risk HeFH before a planned pregnancy	1	B
5. Given that LDL-cholesterol and triglyceride concentrations increase during pregnancy, assessment of plasma lipids and lipoprotein levels should not routinely be considered, unless the results will be used to change management, as in women with HoFH	2	B
6. Bile acid sequestrants should be considered to treat hypercholesterolaemia, ideally 3 months before a planned pregnancy, as well as during pregnancy and lactation; routine monitoring for malabsorption of fat-soluble vitamins (particularly vitamin K with an international normalized ratio) and folate should also be considered	2	B
7. Statins and other systemically absorbed cholesterol-lowering drugs should ideally be discontinued 3 months before planned conception and during pregnancy and lactation. If a woman with FH becomes pregnant while taking a statin, ezetimibe, a PCSK9 inhibitor or other lipid-modifying therapies, this treatment should be stopped, and she should be reassured that this therapy is unlikely to harm the fetus	1	B
8. In women with HoFH and clinical ASCVD, the continued use of statin therapy should be considered; use of statins, ezetimibe, PCSK9 monoclonal antibodies or other lipid-modifying therapies should particularly be considered after the first trimester, especially if the LDL-cholesterol goal is not achieved and lipoprotein apheresis is not available or feasible	2	B
9. Lipoprotein apheresis should be continued or initiated during pregnancy in women with HoFH, especially in those with established ASCVD and in whom LDL-cholesterol levels are not at guideline-recommended goal; similar advice applies to women with severe HeFH, including those with a lipoprotein(a) concentration ≥ 125 nmol/l (≥60 mg/dl)	1	B

ASCVD, atherosclerotic cardiovascular disease; FH, familial hypercholesterolaemia; HeFH, heterozygous familial hypercholesterolaemia; HoFH, homozygous familial hypercholesterolaemia; PCSK9, proprotein convertase subtilisin/kexin type 9.

medicine; these should be adapted to local, regional and national needs, guided by contextual barriers and facilitators, and subjected to regular evaluation.
3. Implementation of improvements in the detection and care of FH should be underpinned by an integrated national cholesterol awareness campaign targeted at young people, high-risk individuals and all health-care professionals.
4. National and regional centres with expertise in lipidology, genetics and ASCVD prevention should be established to accept referrals and give advice, as indicated. All patients with suspected FH should be referred to, or discussed with, a relevant specialist to plan further management and care; a key priority is to establish specialized centres for managing patients with severe FH or HoFH.
5. General practice and primary care should be actively involved in the care of all individuals and families with FH and provide support for screening, diagnosing, managing cholesterol-lowering therapy and addressing comorbidities; regular review and evaluation of health and patient-reported outcomes data are essential.
6. A multidisciplinary team with expertise in caring for individuals with FH should partner with primary care and include representation from appropriate specialty disciplines, including mental health care.

Table 9 | Clinical recommendations on the treatment of familial hypercholesterolaemia by lipoprotein apheresis

Clinical recommendations	Class	Level
1. Lipoprotein apheresis should be undertaken, if feasible, in children (aged ≥3 years and <8 years) and adults with HoFH who do not achieve guideline-recommended LDL-cholesterol goals, despite maximally tolerated, combination drug therapy	1	A
2. Lipoprotein apheresis should be undertaken in adults with phenotypic HeFH and progressive ASCVD who do not achieve LDL-cholesterol goals despite combined treatment with a high-potency statin, ezetimibe and a PCSK9 inhibitor, especially those with a lipoprotein(a) concentration ≥125 nmol/l (≥60 mg/dl)	1	B
3. Vascular access for lipoprotein apheresis should initially be via peripheral veins, but an arteriovenous fistula may be needed if peripheral venous access becomes impossible, which may be particularly relevant to children. Central venous catheters are not recommended except in an emergency or as a temporary measure	1	B
4. Onefold to twofold plasma volumes (body weight in kg × 0.045 l) or blood volumes [plasma volume/(1 − haematocrit)] should be treated weekly or fortnightly in a specialized setting (a lipid clinic, nephrology unit or blood transfusion centre). Plasma exchange requires a smaller extracorporeal blood volume than lipoprotein apheresis and is recommended as an alternative in children with a body weight <30 kg	1	A
5. All diet and drug therapy to lower LDL-cholesterol concentrations should be continued during treatment with lipoprotein apheresis, and comprehensive psychosocial support should be offered to all patients receiving lipoprotein apheresis	1	A
6. Routine full blood counts should be monitored regularly, and iron supplementation initiated if iron-deficiency anaemia develops in patients with FH receiving long-term lipoprotein apheresis	1	A
7. Angiotensin-converting enzyme inhibitors should not be used in patients undergoing lipoprotein apheresis based on apolipoprotein B adsorption, and angiotensin-receptor blocking agents should be substituted	1	A
8. Patients receiving anticoagulants, such as warfarin, will require dose adjustment or discontinuation several days before an apheresis procedure that uses intravenous heparin, but antiplatelet therapy should be maintained. Direct oral anticoagulants (such as apixaban, dabigatran or rivaroxaban) need only be stopped on the day of apheresis because of their shorter half-life	1	B
9. The cholesterol-lowering efficacy of lipoprotein apheresis should be monitored by measuring acute reductions in LDL-cholesterol and lipoprotein(a) concentrations (ideally 65–70%) and by calculating the interval mean (C_{mean}) between consecutive procedures, using the Kroon formula: $C_{mean} = C_{min} + k(C_{max} - C_{min})$, for which C_{max} is the pre-procedure value and C_{min} is the post-procedure value. Values for k are 0.65 for LDL-cholesterol in patients with HoFH and 0.71 for LDL-cholesterol in patients with HeFH receiving statin therapy and undergoing lipoprotein apheresis at fortnightly intervals. Comparison of interval means with the recommended LDL-cholesterol goals for patients with HoFH should be used to adjust the volume of blood or plasma to be treated and/or the frequency of lipoprotein apheresis procedures as necessary	1	B
10. Because the rate of rebound of plasma lipoprotein(a) levels after lipoprotein apheresis is similar to that of plasma LDL-cholesterol levels in patients with HeFH, a value for k of 0.71 in the Kroon formula should be considered appropriate when estimating the interval (intercycle) mean concentration of lipoprotein(a); this value may be used to adjust the lipoprotein apheresis regimen to achieve a therapeutic goal of <90 nmol/l (<43 mg/dl) in patients with elevated lipoprotein(a) concentrations	2	B
11. In children and adults with HoFH and aortic root or coronary artery disease, the effect of lipoprotein apheresis on disease progression should be monitored at least annually by echocardiography or coronary angiography, respectively. The latter procedure is also applicable to patients with HeFH with coronary disease and should be performed as and when indicated	1	B
12. Adjunctive therapy with a PCSK9 inhibitor, either evolocumab or alirocumab, should be attempted in all patients with FH before starting or while receiving lipoprotein apheresis. These therapies will be effective mainly in patients with HeFH and often may replace lipoprotein apheresis. Injected therapeutic agents should be administered soon after, but not immediately before, a lipoprotein apheresis procedure	1	B
13. Adjunctive therapy with lomitapide or evinacumab should be considered in patients with HoFH, particularly in those with progressive ASCVD, who do not reach guideline-recommended LDL-cholesterol goals while receiving lipoprotein apheresis combined with statin, ezetimibe and a PCSK9 inhibitor. This adjunctive therapy increases LDL-cholesterol lowering and may reduce the frequency of lipoprotein apheresis and, if tolerated, sometimes replaces it	2	B
14. When lomitapide or evinacumab is first selected in preference to lipoprotein apheresis, adjunctive use of lipoprotein apheresis should be considered in all patients with HoFH who do not reach guideline-recommended LDL-cholesterol goals	2	B

ASCVD, atherosclerotic cardiovascular disease; FH, familial hypercholesterolaemia; HeFH, heterozygous familial hypercholesterolaemia; HoFH, homozygous familial hypercholesterolaemia; PCSK9, proprotein convertase subtilisin/kexin type 9.

Box 4

Lipoprotein apheresis for familial hypercholesterolaemia

Core implementation strategies:

- Establish a centralized apheresis unit staffed by accredited personnel; use advocacy and peer-support groups
- Assess suitability for treatment by a specialist; offer plasma exchange if lipoprotein apheresis is not available
- Adapt existing infrastructure to widen the clinical availability of apheresis; meet local and regional needs of care
- Establish regular multidisciplinary meetings involving a coalition of specialties that contribute to service delivery
- Use apheresis-specific key performance indicators and patient outcome and experience measures to iteratively improve services
- Participate in networks to share educational, clinical and research experiences; establish a comprehensive clinical quality registry of patients

7. Models of care should ideally consider the entire family as a patient unit. Appropriate strategies for paediatric patients to transition to adult care should be used.
8. Individuals with FH should be active participants in their care and work with their primary care and multidisciplinary team to discuss care pathways.
9. Patient-reported outcome and experience measures form the bedrock of value-based health care and should accordingly be used to improve implementation practice across the continuum of care for FH.
10. The implementation of all clinical recommendations for FH should account, as a priority, for the access to and the acceptability of health services for patients and families of diverse ancestries, including minority groups.
11. Health services should partner with academic and professional organizations and foundations to improve teaching, training and research.
12. When planning and designing treatment protocols across the continuum of care for FH, service providers should seek the collaboration of another clinical centre that provides excellence of care and arrange for relevant staff to visit and train there.
13. All health professionals involved in the care of individuals with FH, including those at the primary care level, should have appropriate accreditation, in addition to ongoing education, training and skills in lipidology, cardiovascular disease prevention, family communication, interpretation of test results, local guidance on data protection, and genomic medicine. Clinical practice guidelines for managing FH should be simplified to improve accessibility and use by all health-care professionals.
14. Digital technologies (telehealth, adherence applications and decision support systems in electronic health records) that target both patients and clinicians should be developed to improve the precision, accuracy and communication of the detection and management of FH.
15. Awareness, advocacy and educational campaigns including social media, website banner advertisements, billboards and/or celebrity endorsements should be conducted to increase public awareness of FH and the importance of genetic testing.
16. Advocacy and peer groups of patients, family members and other stakeholders should be established to support patients with FH and their care, particularly across different sociocultural communities, levels of health literacy and economic circumstances; advocacy for patients with HoFH is crucial for ensuring that health policy addresses all aspects of the care of this most severe form of FH (Supplementary Material 5).
17. Sustainable financing and sharing of existing resources should be used, enabled by key opinion leaders and stakeholder organizations, to deliver an impactful and cost-effective clinical service.
18. The national coding systems for FH should be used in primary and specialist care to improve the precision of data acquisition and linkage and their use for audit, research and development of health policy.
19. A national registry for FH should be established and used for linking patient outcomes, raising awareness, improving advocacy efforts and iteratively auditing key performance indicators, and for international collaborations for improving care.
20. Comprehensive research strategies and programmes, based on the core principles of implementation science, should be developed for evaluating and improving all models of care for FH. This process should focus on the acceptability, adoption, appropriateness, cost, feasibility, fidelity and sustainability of all interventions.

See Box 5 for core general implementation strategies.

Conclusions

Updating models of care meets international calls to action on FH[9,24,25]. This guidance aims to provide comprehensive recommendations for providing the best clinical care for the greatest number of people

Box 5

Core implementation strategies

- Adapt and integrate models of care to local, regional and national needs; develop referral centres of expertise
- Integrate general practitioners with multidisciplinary teams; train and accredit health-care providers in essential skills
- Use shared decision-making for management and patient-reported outcome and experience measures to improve services
- Promote academic–service partnerships, share existing resources and ensure sustainable funding
- Establish a national cholesterol awareness campaign; use advocacy and peer-support groups to improve care
- Use digital health technologies, registries and national coding systems to improve care
- Promote implementation science; develop integrated health-care systems and health policy

with FH worldwide. The recommendations inform both broad and narrow areas of practice across the continuum of care[2,17]. Strong recommendations, mostly informed by high-quality evidence, as well as by common sense, should be followed as best practice, whereas the weaker recommendations are optional and provide a basis for further research[2,16,17,36,289] (for references supporting recommendations, see Supplementary Material 6). Because of economic, political, cultural and social differences among countries, the recommendations we make might not be universally applicable or adopted.

Nevertheless, exponential growth in new knowledge on the diagnosis and effective therapies for FH[2] has set a precedence for countries to aspire to developing high-quality, integrated health-care systems for FH[2,9,23–25]. A challenge for health-care organizations is adapting to the demands of the complexities of changes required[2]. Implementation science provides the best methodology to address this challenge and was, therefore, used to support the clinical recommendations[29,30,32,280].

However, evaluating implementation practice, including patient-reported outcomes and experiences, is an ongoing challenge for evolving models of care for patients with FH[29,32,37,280]. Beyond observational investigations, future implementation research on FH should involve interventional studies, ideally based on randomized, stepped-wedge, hybrid, counterbalanced and adaptive designs[32,279,287]. Researchers should make particular efforts to include subjects from diverse socioeconomic strata, ancestries and geographical location. These studies would increase generalizability and allow replication of findings across different real-world settings. The development and utilization of integrated care systems to improve the health outcomes of all patients with FH remains a global challenge for implementation programmes[290].

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