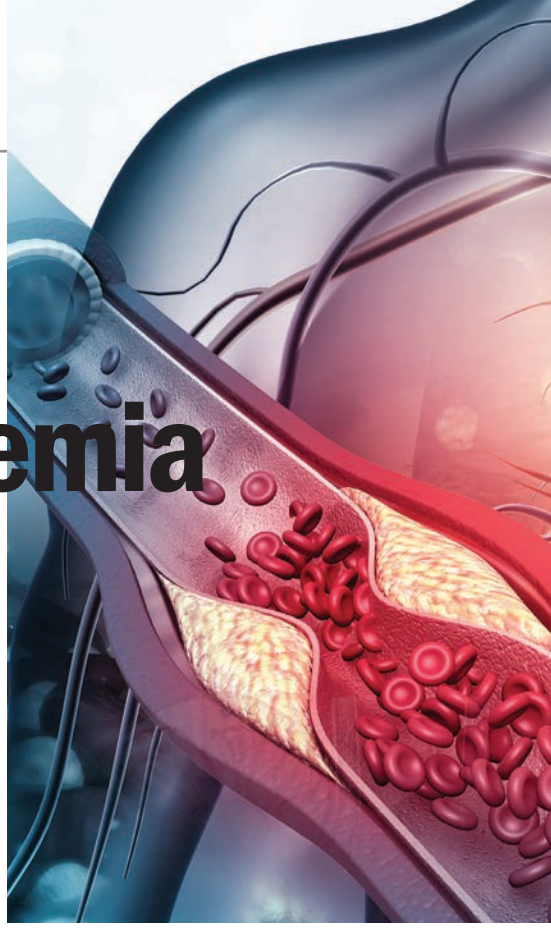

Familial hypercholesterolaemia

Enhancing the care of patients and families

NICK S.R. LAN MB BS(Hons), MClinUS, MClinRes(Dist); **JING PANG** PhD
GERALD F. WATTS DSc, PhD, MD, FRCP, FRACP

Familial hypercholesterolaemia (FH) is a common genetic disorder of LDL-cholesterol, that, if untreated, leads to premature atherosclerotic cardiovascular disease (ASCVD). With early diagnosis and initiation of cholesterol-lowering treatment, the risk of ASCVD can be substantially reduced. Yet, many people with FH remain undiagnosed and undertreated. GPs can play an important role in the care of patients and families with FH.

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Dr Lan is a Cardiology Advanced Trainee in the Departments of Internal Medicine and Cardiology, Royal Perth Hospital; and a Clinical Senior Lecturer in the School of Medicine, University of Western Australia, Perth. Dr Pang is a Research Fellow in the School of Medicine, University of Western Australia, Perth. Professor Watts is Senior Consultant Physician in the Departments of Internal Medicine and Cardiology, Royal Perth Hospital, Perth; and Winthorp Professor of Cardiometabolic and Internal Medicine at the University of Western Australia, Perth, WA.

Familial hypercholesterolaemia (FH) is an autosomal dominant and highly penetrant genetic disorder affecting the LDL receptor pathway. FH is characterised by lifelong elevated plasma LDL-cholesterol (LDL-C) levels due to impaired hepatic clearance, and by an increased risk of atherosclerotic cardiovascular disease (ASCVD), particularly coronary artery disease.[1] Heterozygous FH is one of the most common monogenic conditions, with an estimated prevalence of one in 250 people worldwide.[2] Some ethnic groups may have a higher frequency of FH due to gene founder effects, including the Afrikaans, Christian Lebanese and French Canadian populations. In Australia, there are about 100,000 people living with FH.[3] Compared with the general population, the risk of coronary artery disease may be over 10-fold higher in patients with heterozygous FH.[4,5] Homozygous or compound heterozygous FH has an estimated prevalence of one in 160,000 to 300,000 people and manifests as very elevated levels of LDL-C (typically >10 mmol/L), with severe ASCVD and aortic valve sclerosis often present by the late teenage years, or earlier if untreated.[6]

The major driver of ASCVD risk in people with FH is the cumulative exposure to elevated plasma LDL-C levels from birth (Figure 1).[7] Early initiation of lifestyle measures and medications to reduce LDL-C levels in people with FH can effectively reduce the risk of ASCVD.[8] However, most people with FH remain undiagnosed and undertreated, representing a missed opportunity for ASCVD prevention and a major public health problem.[9] GPs request more than 90% of LDL-C measurements and 88% of Australians present to GPs annually.[10,11] A survey of Australian GPs showed that most considered they were the most effective health practitioners for managing FH.[12]

KEY POINTS

- Familial hypercholesterolaemia (FH) is a common genetic disorder of the LDL receptor pathway, with the heterozygous form affecting one in 250 individuals.
- A diagnosis of FH should be suspected in people with an elevated LDL-cholesterol (LDL-C) level (>5 mmol/L), especially if there is a personal or family history of premature coronary artery disease.
- The Dutch Lipid Clinic Network Criteria can be used to make a phenotypic diagnosis of FH; however, it should not be used in children.
- Genetic testing plays a role in confirming the diagnosis (MBS item 73352), atherosclerotic cardiovascular disease risk stratification and cascade testing (MBS item 73353).
- Because FH is an autosomal dominant condition, cascade testing is important to identify undiagnosed relatives of index cases.
- High-intensity statins remain the cornerstone of therapy; however, the addition of ezetimibe and monoclonal antibodies targeting PCSK9 may be required to attain LDL-C goals.
- A multidisciplinary approach and integration of services are required to implement optimal care of patients and families with FH.

GPs are ideally placed to enhance the care of patients and families with FH.[11] The purpose of this article is to provide a contemporary overview of the diagnosis and management of FH.

Screening

FH meets all criteria for screening for a condition. Several strategies for universal, targeted, systematic and opportunistic screening have been proposed to detect probands (i.e. the first person diagnosed with FH in a kindred).[13] Examples of FH screening strategies (Table 1) include universal screening of children at the time of immunisations coupled with 'reverse' cascade testing of parents if the child is found to have the condition, targeted screening of patients with premature ASCVD in coronary care units or rehabilitation programs, application of electronic tools to systematically search GP patient databases, and interpretative comments and alerts on lipid profile results issued by pathology laboratories.[13,14]

Opportunistic screening of adults, such as during a health check, should be employed in primary care to detect FH, based on an LDL-C level above 5 mmol/L.[3] Owing to practical advantages, nonfasting samples can be considered for FH screening but should be used with caution in patients with hypertriglyceridaemia

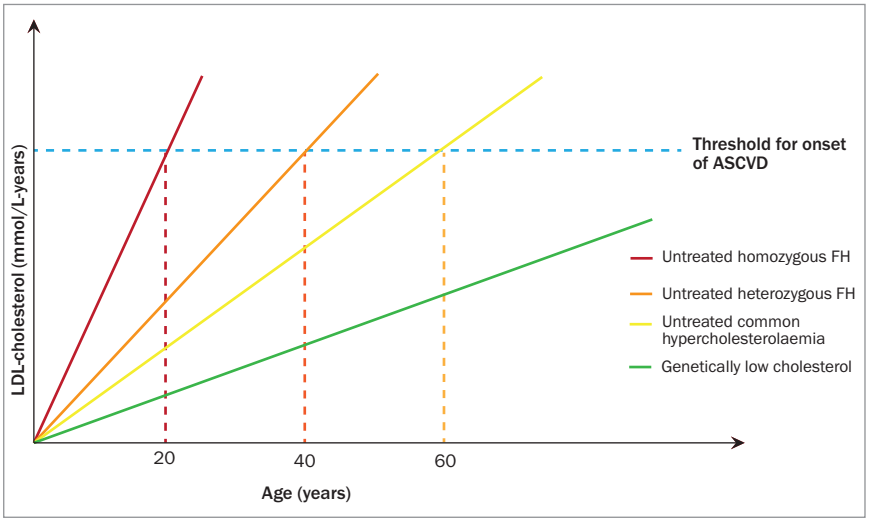


Figure 1. Time course for the onset of ASCVD. The solid lines represent different plots of cumulative LDL-C with age in individuals with varying risk of ASCVD, with the threshold for onset represented by the dashed horizontal line. Patients with untreated homozygous FH have the steepest slope of LDL-C versus age (red line) and experience earlier onset of ASCVD compared with those with untreated heterozygous FH (orange line) or untreated common hypercholesterolaemia (yellow line). Individuals with genetically low cholesterol from birth have a markedly reduced risk of developing ASCVD (green line).

Abbreviations: ASCVD = atherosclerotic cardiovascular disease; FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol.

Adapted from Shapiro MD, Bhatt DL. J Am Coll Cardiol 2020; 29: 1517-1520.[7]

TABLE 1. SCREENING STRATEGIES FOR FAMILIAL HYPERCHOLESTEROLAEMIA

Screening strategy	Features
Opportunistic screening for family history and lipid profile	• Patients with a positive family history have their plasma lipid profile measured and are examined for clinical features of FH • Patients with high LDL-C levels (>4.9 mmol/L for adults and >4.0 mmol/L for children) are reviewed for family history and clinical features of FH
Opportunistic alerts and interpretative comments on pathology reports	Flagging of LDL-C higher than 5.0 mmol/L on pathology reports to alert GPs and suggest referral to a specialist for assessment
Targeted screening of high-risk coronary patients in secondary and tertiary centres	Targeted screening in: • patients younger than 60 years of age presenting to coronary care, stroke, cardiothoracic and vascular units • patients attending cardiac rehabilitation programs
Systematic searching of medical records	Search of electronic records and systematic selection of medical notes to identify potential index cases
Universal screening of newborns	Integrating FH testing into the newborn screening programs
Universal screening of children	Universal screening of children, where all children at a certain age have their lipid levels measured; for example, at time of immunisation
Population screening of young adults	Offer DNA testing to all young adults for a range of preventable conditions
Cascade screening (or testing) of family members	• Systematic screening of blood relatives of index cases with a definite diagnosis of FH. This usually starts after identification of an adult with FH • 'Reverse cascade screening' is when a child is first identified, and family members are subsequently tested

Abbreviations: FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol.

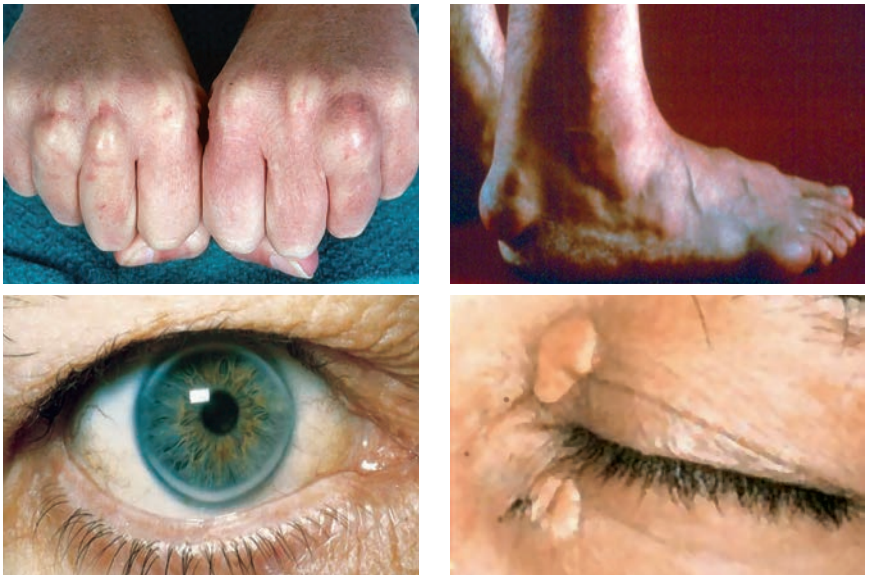


Figure 2. Florid examples of physical signs of familial hypercholesterolaemia. Tendon xanthomata (white or yellow lumps of cholesterol deposits) around the knuckles (a, top left) and Achilles tendon (b, top right); corneal arcus (a circular deposit of cholesterol at the edge of the cornea; c, bottom left); and xanthelasma (a yellow deposit of cholesterol around the eyelid or medial canthus area; d, bottom right).

Reproduced with permission from The Royal Australian College of General Practitioners from: Brett T, Arnold-Reed DE. Familial hypercholesterolaemia: a guide for general practice. Aust J Gen Pract 2019; 48: 650-652. Available online at: www1.racgp.org.au/ajgp/2019/september/familial-hypercholesterolaemia.

(triglyceride level >4.5 mmol/L), who should have fasting samples tested.[3] It has also been advocated that FH be considered part of the newborn bloodspot screening program in Australia; however, such a strategy needs further development.[15] Recommended ages for screening children for FH are as early as possible (no later than 2 years) for suspected homozygotes and from the age of 5 years (no later than 10 years) for suspected heterozygotes.

Providing educational resources and national programs to raise awareness among the public and health professionals about the health impacts of high cholesterol, and FH specifically, are also important.[16] The FH Australasia Network provides online resources on FH (https://www.athero.org.au/fh/).

Phenotypic diagnosis

FH can be diagnosed using criteria combining personal and family history of hypercholesterolaemia and premature

ASCVD, LDL-C levels and physical signs of cholesterol deposition, such as tendon xanthoma, arcus cornealis and xanthelasma (Figure 2).[17-20] Physical stigmata can be subtle and are less prevalent due to statin therapy. Thus, their absence does not exclude the diagnosis of FH.[21] Although several diagnostic tools are available, the Dutch Lipid Clinic Network Criteria score (DLCNC) (Table 2) is the preferred tool in Australia for adults.[3,22] The DLCNC tool assigns a score to each diagnostic criterion and the total score is used to categorise the likelihood of FH as 'definite', 'probable', 'possible' or 'unlikely'. In patients taking a statin or ezetimibe, the pretreatment LDL-C level can be estimated using a correction factor.[23]

In children, the clinical diagnosis of FH relies on LDL-C levels and family history. Testing for suspected heterozygous FH using a phenotypic and/or a genotypic strategy should be considered in children between the ages of 5 and 10 years.[3] The DLCNC tool is not suitable for children.[21] A probable diagnosis of FH should be considered in children with an LDL-C level higher than:[21,24]

- 5.0 mmol/L in the absence of parental history of hypercholesterolaemia or premature ASCVD
- 4.0 mmol/L with parental history of hypercholesterolaemia or premature ASCVD
- 3.5 mmol/L with a parent with a pathogenic or likely pathogenic gene variant.

If FH is suspected, a fasting plasma or serum lipid profile should be performed, ideally on two occasions, in both adults and children, and secondary causes of hypercholesterolaemia, such as hypothyroidism, nephrotic syndrome, cholestatic liver disease and medication use (e.g. steroids, isoretinoids), excluded.[3] After a diagnosis is made, patients with FH should be referred to, or discussed with, a specialist with expertise in lipidology.[3]

TABLE 2. DUTCH LIPID CLINIC NETWORK CRITERIA[22]*

Criteria	Score†
Family history	
• First-degree relative with known premature coronary or vascular disease;‡ or • First-degree relative with known LDL-C above the 95th percentile for age and sex	1
• First-degree relative with tendinous xanthomata or arcus cornealis; or • Children younger than 18 years with an LDL-C level above the 95th percentile for age and sex	2
Clinical history	
Patients with premature coronary artery disease‡	2
Patients with premature cerebral or peripheral vascular disease‡	1
Physical examination	
Tendinous xanthomata	6
Arcus cornealis before 45 years of age	4
Untreated LDL-C (mmol/L)	
LDL-C ≥8.5	8
LDL-C 6.5–8.4	5
LDL-C 5.0–6.4	3
LDL-C 4.0–4.9	1
Score: definite FH: ≥8; probable FH: 6–8; possible FH: 3–5; unlikely FH: <3	

Abbreviations: FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol.
* The Dutch Lipid Clinical Network Criteria calculator can be accessed online (https://www.athero.org.au/fh/calculator/).
† Only the highest score in each section is chosen to add up to the total score, to a maximum of 18.
‡ Men younger than 55 years and women younger than 60 years.

Genetic testing

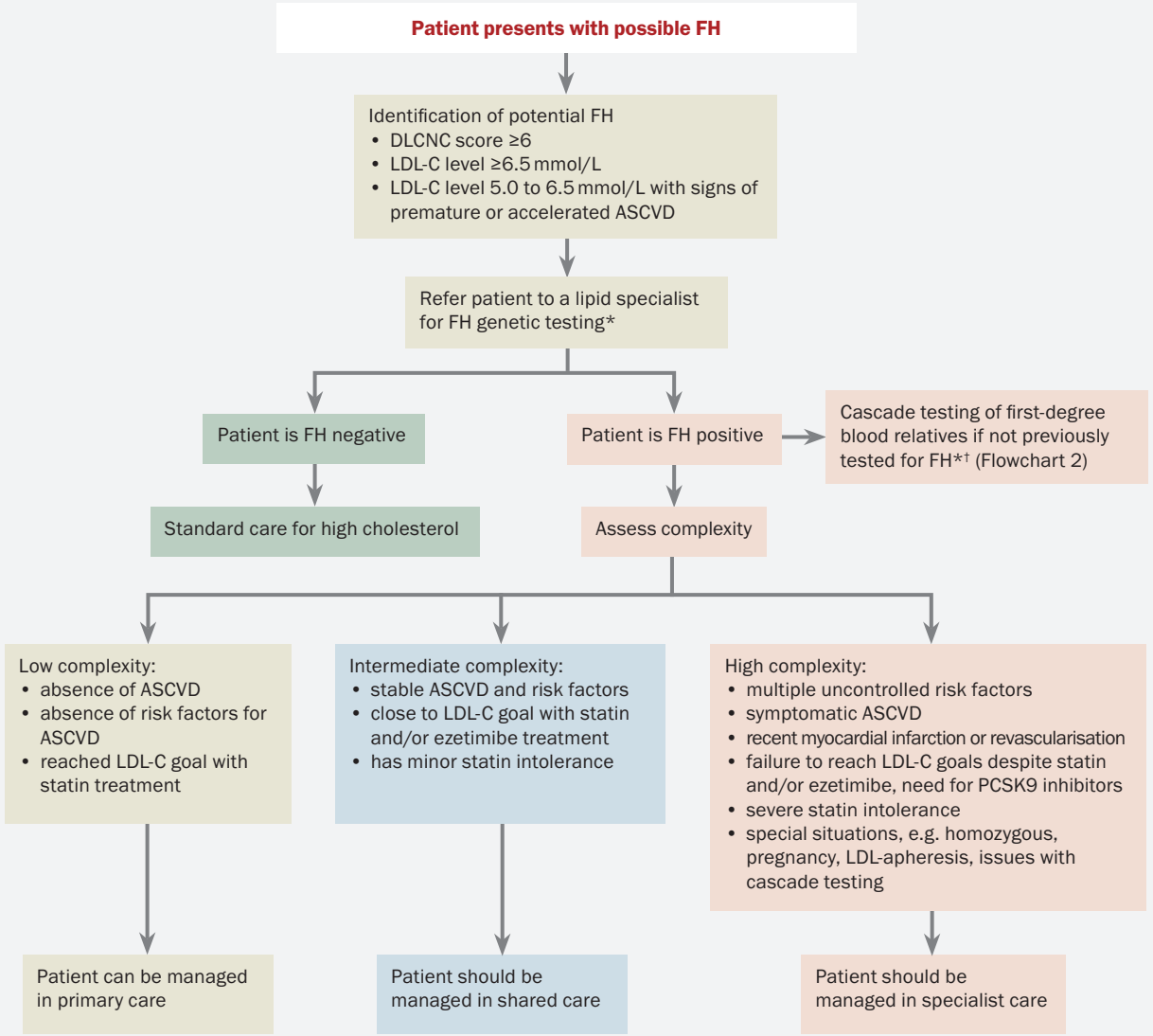
Genetic testing is the gold standard for diagnosing FH and should be offered when available.[3] However, the absence of a causative variant does not exclude the diagnosis, especially when the phenotypic expression is strong.[25] Pathogenic gene variants are detected in 60 to 80% of those with 'definite' FH and in 20 to 40% with 'probable' FH.[25] Variants in the LDL receptor (*LDLR*), apolipoprotein B (*APOB*) and proprotein convertase subtilisin/kexin type 9 (*PCSK9*) genes contribute to more than 95% of genetically confirmed cases. There is also a very rare form of autosomal recessive FH due to variants in the LDL receptor adaptor protein 1 (*LDLRAP1*) gene.[26,27] Patients with phenotypic FH, but without a detectable FH-causing variant, may have an unidentified genetic variant or polygenic hypercholesterolaemia.[25]

Genetic testing remains underutilised, despite its value in:[25,28]

- increasing the specificity of diagnosis
- enabling more efficient genetic counselling
- improving the accuracy of risk stratification
- improving adherence to treatment
- enabling access to special therapies.

Genetic testing should ideally be offered to adult index cases with a definite or probable diagnosis of FH by the DLCNC and be performed using accredited methods in certified laboratories.[3] The MBS has introduced new pathology services to facilitate genetic testing for FH-causing variants in index cases (MBS item 73352), which requires non-GP specialist authorisation.[11,29]

1. GENETIC TESTING AND MANAGEMENT OF PATIENTS WITH FAMILIAL HYPERCHOLESTEROLAEMIA



Abbreviations: ASCVD = atherosclerotic cardiovascular disease; DLCNC = Dutch Lipid Clinic Network Criteria; FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol; MBS = Medicare Benefits Schedule; PCSK9 = proprotein convertase subtilisin/kexin type 9.

* The MBS offers genetic testing for FH-causing variants for index cases (MBS item 73352) and cascade testing for first- and second-degree relatives (MBS item 73353).

† Genetic cascade testing may be undertaken by a specialist lipid clinic in collaboration with a GP.

Adapted from Vickery AW, et al. Heart Lung Circ 2014; 23: 1158-1164.[29]

One of the major benefits of genetic testing for FH is to enable cascade testing of at-risk family members. If an index case has a pathogenic FH-causing variant, cascade genetic testing of first- or second-degree relatives should be offered, and GPs can request this (MBS item 73353).[11]

Pre- and post-test counselling is an integral part of the process for FH genetic testing and should be delivered by a healthcare professional with skills in genetic counselling.[25] Information for GPs on genetic counselling is available through the WA HealthPathways (https://wa.communityhealthpathways.org/981755.htm). A shared-care approach between GP and non-GP specialists can facilitate genetic testing of index cases and cascade testing.[29] An algorithm for genetic testing and management of patients with FH is presented in Flowchart 1.

Cascade testing

Cascade testing is the systematic testing of blood relatives of an index case with the condition.[30] Since FH is a monogenic autosomal dominant genetic disorder with high penetrance, 50% of first-degree relatives of index cases will have the condition (Figure 3).[14,25,31] After FH is diagnosed in an index case, cascade testing of first- and second-degree relatives should be offered using phenotypic (i.e. LDL-C levels) and genotypic (MBS item 73353) approaches where feasible. An approach to cascade testing of biological relatives of a patient with confirmed FH is summarised in Flowchart 2.[3,31] Genetic testing should be offered to diagnose FH in children after a pathogenic or likely pathogenic gene variant has been identified in a parent or first-degree relative.[3,21] Cascade genetic testing also identifies relatives who do not inherit the genetic variant, which gives reassurance that they do not have FH.[25]

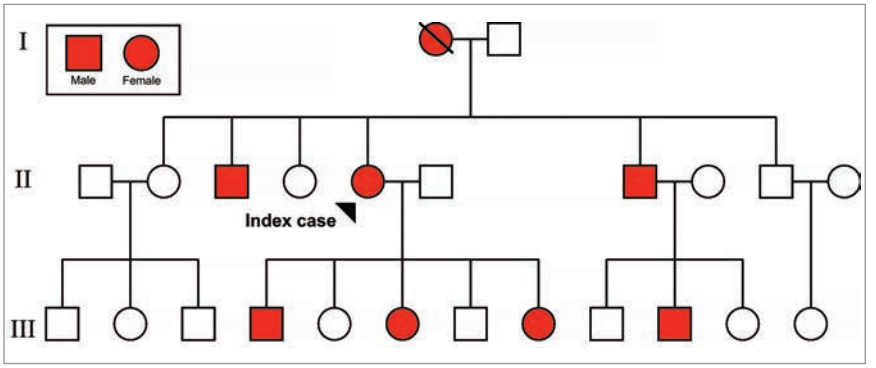
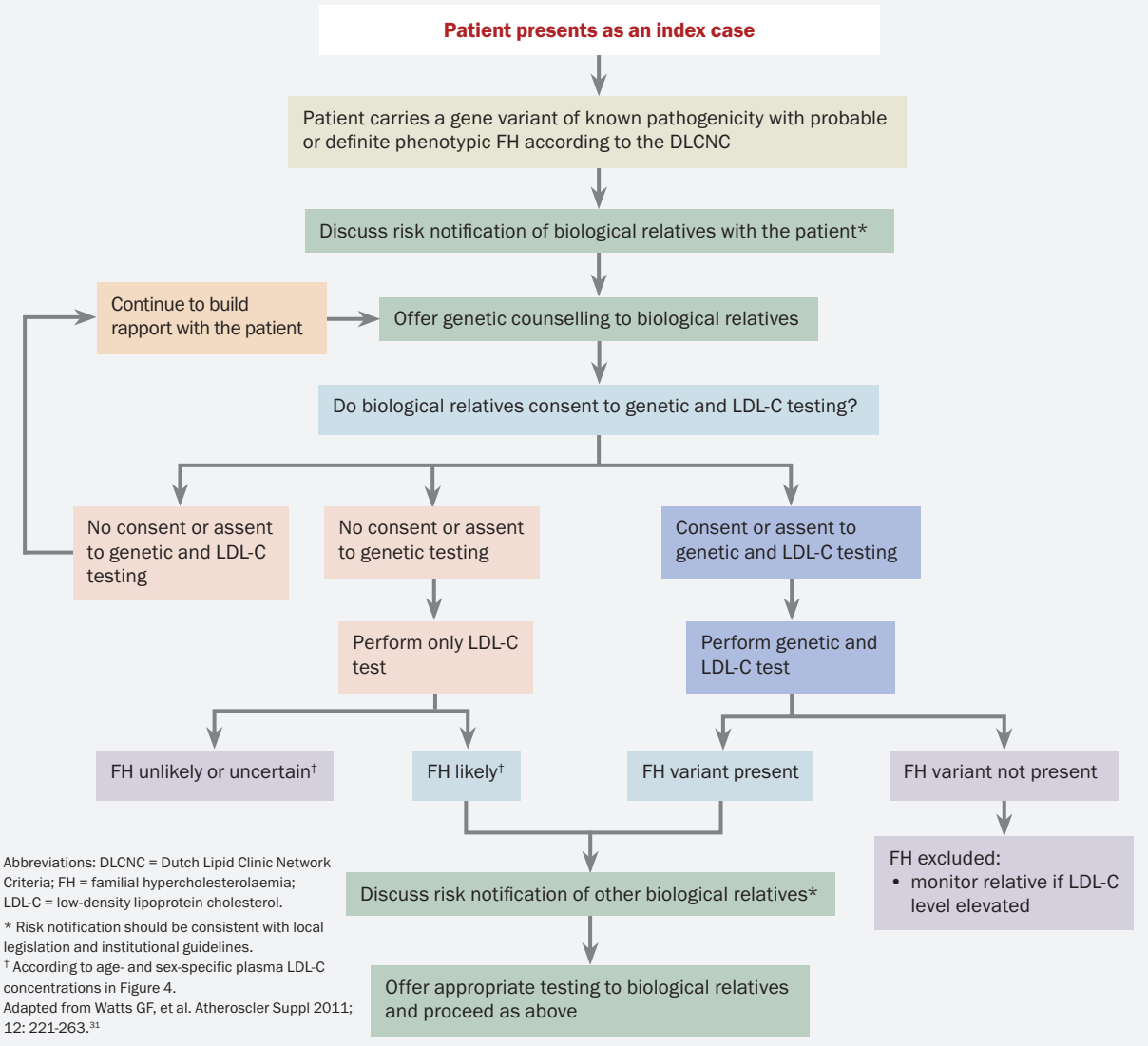


Figure 3. An example family pedigree depicting the autosomal dominant inheritance of familial hypercholesterolaemia.[31]

Cascade screening programs that use variant-specific genetic testing have been shown to be feasible and cost-effective.[32] However, cascade testing should ideally be co-ordinated by a well-resourced centre that can also enable testing via GPs.[3] Risk notification of family members should be performed according to local legislation and institutional guidelines.[3] As with genetic testing of index cases, pre- and post-test counselling for genetic cascade screening should be delivered by a healthcare professional with skills in genetic counselling.[25] In the absence of genetic testing, cascade testing of relatives of index cases may be carried out using measurement of fasting

2. CASCADE TESTING OF BIOLOGICAL RELATIVES OF A PATIENT WITH CONFIRMED FAMILIAL HYPERCHOLESTEROLAEMIA



Abbreviations: DLCNC = Dutch Lipid Clinic Network Criteria; FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol.

* Risk notification should be consistent with local legislation and institutional guidelines.

† According to age- and sex-specific plasma LDL-C concentrations in Figure 4.

Adapted from Watts GF, et al. Atheroscler Suppl 2011; 12: 221-263.[31]

LDL-C, with age-and gender-specific levels (Figure 4); the DLCNC should not be used to make the diagnosis of FH in relatives.[3,25,33]

ASCVD risk stratification

After FH is diagnosed, a comprehensive ASCVD risk assessment should be conducted to develop a personalised treatment plan and guide management.[34] Traditional ASCVD risk factors remain significant predictors of ASCVD in patients with FH, highlighting the importance of a multifactorial approach to risk reduction.[35,36] In women, female-specific ASCVD risk factors, such as hypertension or toxaemia in pregnancy, gestational diabetes and premature menopause, should be considered. Tendon xanthomata reflect cumulative exposure to elevated plasma LDL-C levels and are associated with higher ASCVD risk.[37] Furthermore, lipoprotein(a) [Lp(a)] is a genetically determined LDL-like particle bound to apolipoprotein(a) that is a causal risk factor for ASCVD and calcific aortic valve stenosis.[38] In patients with FH, an elevated Lp(a) level is common and is a potent risk factor for coronary artery disease; it may also mimic the FH phenotype diagnostically, especially when markedly elevated or if coexisting with common hypercholesterolaemia.[38,39] Measurement of Lp(a) should be considered as part of routine evaluation, noting that an MBS item is not yet available and that

out of pocket costs may be incurred. However, Lp(a) measurement is a one-off test, as Lp(a) levels are considered stable throughout a person's lifetime.[40] Genetic testing provides information on ASCVD risk, as the presence of a pathogenic gene variant is associated with a higher cumulative exposure to LDL-C and is predictive of ASCVD.[41]

Primary prevention ASCVD risk calculators for the general population (such as the Australian CVD Check or the Framingham Risk Score) should not be used in patients with FH, as lifelong exposure to elevated LDL-C levels are not considered, thus risk will be underestimated.[42] FH-specific equations for absolute ASCVD risk have been developed for people with genetically confirmed FH. For instance, the Spanish Familial Hypercholesterolemia Cohort Study risk equation (SAFEHEART-RE) takes into account age, sex, previous ASCVD, hypertension, obesity, smoking, LDL-C levels and Lp(a) levels; however, requires further validation in an Australian population.[43]

Noninvasive imaging for atherosclerosis, such as carotid ultrasonography, coronary artery calcium scoring and CT coronary angiography, can facilitate personalised risk assessment; it enables the identification of patients with atherosclerotic disease who may require more intensive treatment, including referral for further cardiac evaluation.[42] Patients with symptoms of ASCVD should be referred to a cardiologist for further investigation and management.

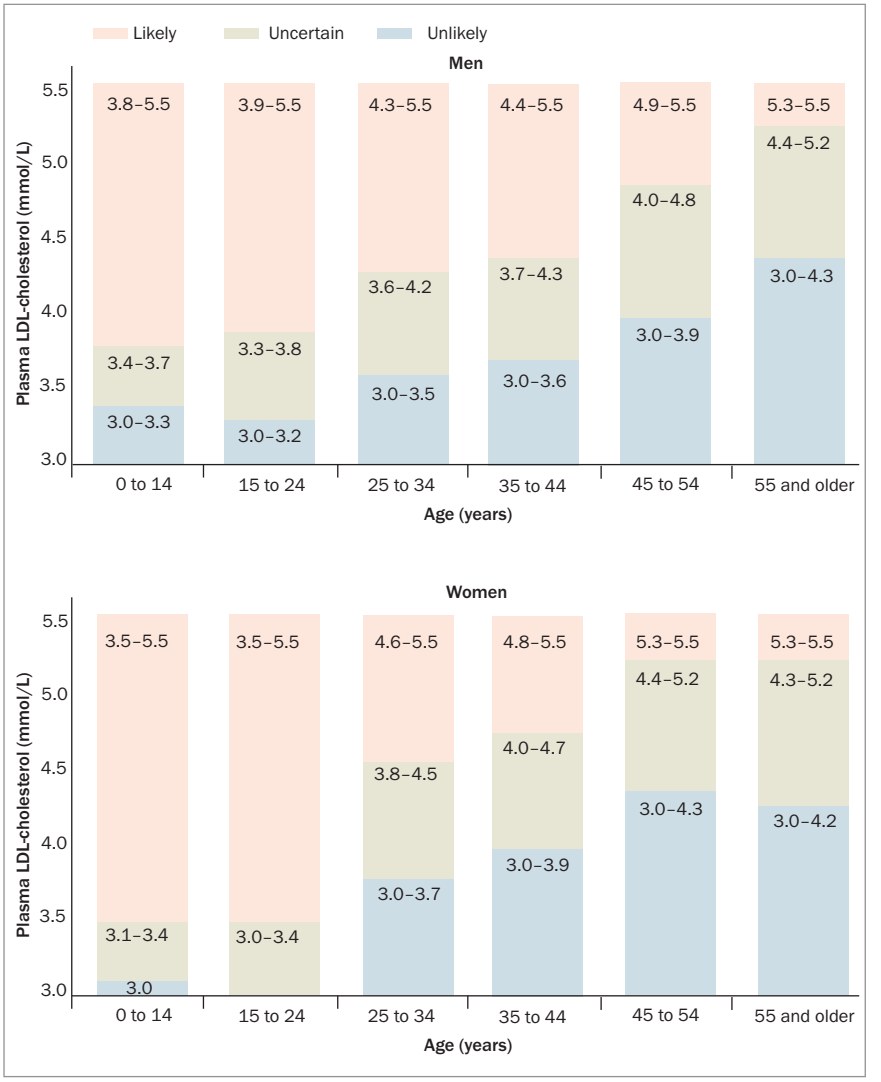


Figure 4. Age- and sex-specific thresholds for making a phenotypic diagnosis of familial hypercholesterolaemia (FH) during cascade testing. When genetic testing is not feasible, the diagnosis of FH in close relatives during cascade testing should be made phenotypically using age- and sex-specific LDL-C levels. The Dutch Lipid Clinic Network Criteria should not be used.
Adapted from Starr B, et al. Clin Chem Lab Med 2008; 46: 791-803.[33]

Lifestyle modifications and management of non-cholesterol risk factors

Modifications targeting a heart-healthy diet, smoking cessation, regular exercise, weight loss, moderation in alcohol consumption and mitigation of psychological stress are emphasised by all guidelines for the prevention of ASCVD and are recommended for all patients with FH.[3] Hypertension, diabetes and obesity should be managed according to relevant guidelines. The recommended cardioprotective diet for patients with FH is one that is low in saturated fat and cholesterol, coupled with the preference for unsaturated fat, particularly within the context of the Mediterranean-style or DASH-style (Dietary Approaches to Stop Hypertension) dietary patterns.[44] Referral to a dietitian for specialised advice is recommended.[3,45] However, a heart-healthy diet alone does not usually provide adequate reduction of LDL-C levels in patients with FH. Nutraceutical regimens, including plant sterols, red yeast rice, soluble fibre and berberine, may be useful adjunctive therapies in certain patients.[3,46,47]

Pharmacotherapy for lowering LDL-cholesterol

Based on extensive clinical trial, registry and genetic data, cholesterol lowering with statins remains the mainstay therapy for

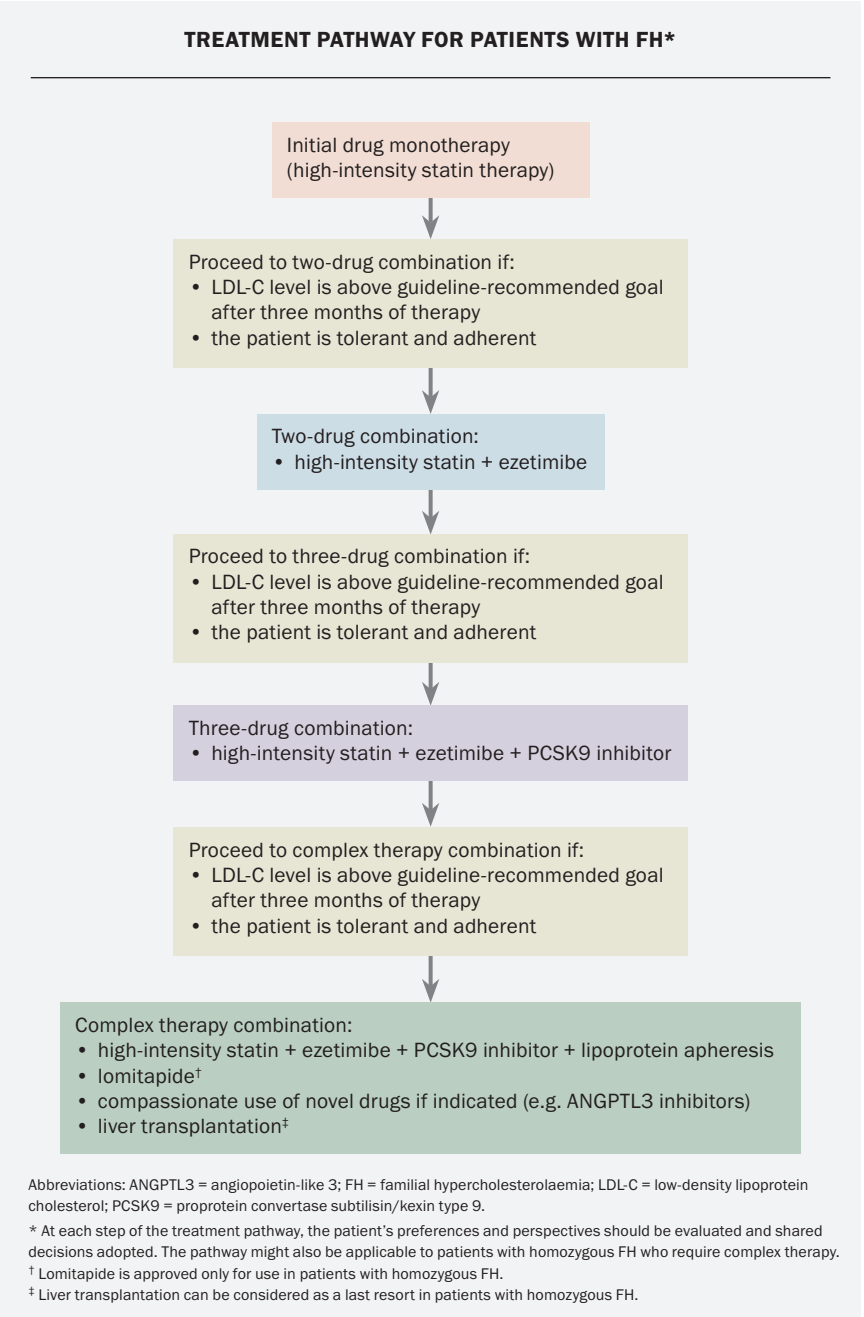


Figure 5. Treatment pathway for patients with familial hypercholesterolaemia.
Adapted from Watts GF, et al. Nat Rev Cardiol 2020; 17: 360-377.[34]

reducing the cumulative burden to elevated LDL-C levels and to prevent ASCVD.[48]

Adults with heterozygous FH

In adults with heterozygous FH, high-potency statins (such as high-dose atorvastatin or rosuvastatin) should be initiated as soon as possible after the diagnosis, with shared decision making to improve adherence. According to the FH Australasia Network guidelines, the LDL-C goal for adults with FH is a greater than 50% reduction in LDL-C levels and either an LDL-C level below:[3]

- 2.5 mmol/L in the absence of ASCVD or other major ASCVD risk factors
- 1.8 mmol/L if there is imaging evidence of ASCVD or if other major ASCVD risk factors are present
- 1.4 mmol/L if there is clinical ASCVD.

However, statins alone are often insufficient to attain LDL-C goals in most patients and sequential addition of other therapies is needed (Figure 5).[34,49] The addition of ezetimibe (a cholesterol absorption inhibitor) can further reduce LDL-C levels by up to 20%. It is recommended as add-on therapy, or as monotherapy in those who are statin-intolerant, with good safety and efficacy and low cost.[50,52] Bile acid sequestrants modestly reduce LDL-C levels but are seldom used, owing to gastrointestinal adverse effects.[52] Bempedoic acid (an adenosine triphosphate citrate lyase inhibitor) is well tolerated and can be considered in patients who are statin-intolerant; however, it is not yet available in Australia.[53] Statin intolerance is an important issue and should be managed according to established guidelines.[54]

Therapies targeting PCSK9 (a protein that binds to the LDL receptor resulting in degradation of the receptor) are also available.[55] Inhibition of PCSK9 leads to upregulation of LDL receptor activity, thereby lowering plasma LDL-C levels. The PCSK9 inhibitors alirocumab and evolocumab are fully human monoclonal antibodies that are usually administered subcutaneously every two weeks. They lower LDL-C levels by 50 to 60% and reduce CVD events when added to statin therapy.[56,57] These agents are safe and efficacious in patients with FH, with injection site reactions being the main adverse effect.[58-62] Accordingly, these agents are recommended as third-line therapy after statins and ezetimibe.[3] Monoclonal antibodies targeting PCSK9 are reimbursed on the PBS for patients with FH and can be initiated by GPs in consultation with a specialist.[3]

Pregnancy and FH

Women of child bearing age should be offered individualised prepregnancy counselling and contraception advice, as statins are associated with risk of teratogenesis.[3] Safe and reliable forms of contraception should be recommended during statin treatment. Statins and other systemically absorbed cholesterol-lowering medications should be ceased three months prior to planned conception and during pregnancy and breastfeeding.[3] However, prolonged periods off cholesterol-lowering treatment due to conception planning, pregnancy and breastfeeding may increase ASCVD risk.[63] In pregnant women with FH, the severity of hypercholesterolaemia, presence of ASCVD and risks and benefits of cholesterol-lowering therapies need to be considered.[64] Bile acid sequestrants are safe to use in pregnancy but can affect absorption of fat-soluble vitamins, such as vitamin K.[64] Additionally, lipoprotein apheresis can be performed safely during pregnancy, and may be required for patients with homozygous FH or severe heterozygous FH, depending on ASCVD risk.[65] A multidisciplinary approach involving experienced lipidologists, obstetricians and cardiologists should be followed.[3]

Children with heterozygous FH

In children with FH, modest and sustained reductions in LDL-C levels have a major impact in preventing ASCVD.[21,24] Statins licensed for this age group (pravastatin, fluvastatin and simvastatin) should be initiated after age 8 to 10 years.[3] An LDL-C goal below 3.5 mmol/L or a 50% reduction in LDL-C levels can be considered for children older than 10 years with FH.[3,21] Studies have shown that statins are safe and efficacious in children with FH, with 20-year observational follow-up data showing a reduction in ASCVD events and death from ASCVD.[66,67] Ezetimibe and monoclonal antibodies targeting PCSK9 are approved for patients older than 10 years with FH, with recent studies showing their safety and efficacy.[68-71] Weight, growth, physical and sexual development, and wellbeing should be monitored in children receiving cholesterol-lowering therapies.[3,21] Children with FH should preferably be reviewed by a paediatrician with expertise in lipidology.[3,21] A multidisciplinary approach founded on shared decision making with the parents and an all-inclusive approach should be undertaken, addressing barriers and enablers to treatment. Transition clinics from childhood to adulthood are recommended, and should be planned well in advance.[3,21]

Children and adults with homozygous FH

Patients with homozygous FH should be referred to specialist centres as management is substantially more difficult.[3] In children and adults with homozygous FH, statins should be initiated as soon as possible after the diagnosis.[3] Ezetimibe and monoclonal antibodies targeting PCSK9 can be used; however, response to treatment may be reduced in patients carrying LDLR-negative variants who have minimal or no residual LDL-receptor function.[62] Lipoprotein apheresis may therefore be required to attain adequate reduction in LDL-C levels and has been performed safely in children.[65] Apheresis is performed weekly or every two weeks, with adequate vascular access and appropriately trained staff being essential.[65] Barriers include lack of availability, high cost, expertise required, patient inconvenience and adverse effects. Other therapies for patients with homozygous FH include lomitapide (a microsomal triglyceride transfer protein inhibitor) and evinacumab (a monoclonal antibody targeting angiopoietin-like 3 protein); both work independently of LDL-C receptor function but require specialist consultation as they are obtained via special access or compassionate use schemes.[72,73] Liver transplantation may be considered as a very last resort for patients with homozygous FH; however, it has rarely been performed in Australia.[74]

On the horizon

Inclisiran is a double-stranded small interfering ribonucleic acid therapy that inhibits hepatic synthesis of PCSK9. Inclisiran is administered subcutaneously every six months and can reduce LDL-C levels by 40 to 50% in patients with heterozygous FH, with the main adverse effects being injection site reactions and nasopharyngitis.[75,76] Bempedoic acid may also play a role in the management of FH, as it has been shown to lower LDL-C levels by about 20% and reduce ASCVD events in patients with statin intolerance and ASCVD or ASCVD risk factors.[53] Several novel cholesterol-lowering agents are also in clinical development.[77]

Conclusion

FH is a common genetic disorder that GPs will encounter in their practice. GPs can play a central role in the continuity of care of patients with FH, spanning screening, diagnosis, cascade testing, ASCVD risk stratification and lipid management. Earlier diagnosis and initiation of effective cholesterol-lowering treatments is required to reduce the burden of ASCVD in patients and their families with FH. Advances in cholesterol-lowering therapies have provided strategies that allow more patients with FH to approach recommended treatment goals. Effective implementation of FH care requires an integrated health system approach, with shared care between GPs and other specialities. MT

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A list of references is included in the online version of this article (www.medicinetoday.com.au).

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