Familial hypercholesterolaemia: A model of care for Australasia

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1 See Appendix 1.

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Abstract

Familial hypercholesterolaemia (FH) is a dominantly inherited disorder present from birth that causes marked elevation in plasma cholesterol and premature coronary heart disease. There are at least 45,000 people with FH in Australia and New Zealand, but the vast majority remains undetected and those diagnosed with the condition are inadequately treated.

To bridge this major gap in coronary prevention the FH Australasia Network (Australian Atherosclerosis Society) has developed a consensus model of care (MoC) for FH. The MoC is based on clinical experience, expert opinion, published evidence and consultations with a wide spectrum of stakeholders, and has been developed for use primarily by specialist centres intending starting a clinical service for FH. This MoC aims to provide a standardised, high-quality and cost-effective system of care that is likely to have the highest impact on patient outcomes.

The MoC for FH is presented as a series of recommendations and algorithms focusing on the standards required for the detection, diagnosis, assessment and management of FH in adults and children. The process involved in cascade screening and risk notification, the backbone for detecting new cases of FH, is detailed. Guidance on treatment is based on risk stratifying patients, management of non-cholesterol risk factors, safe and effective use of statins, and a rational approach to follow-up of patients. Clinical and laboratory recommendations are given for genetic testing. An integrative system for providing best clinical care is described.

This MoC for FH is not prescriptive and needs to be complemented by good clinical judgment and adjusted for local needs and resources. After initial implementation, the MoC will require critical evaluation, development and appropriate modification.

Abbreviations: ABI, ankle brachial index; ACE, angiotensin converting enzyme; ALT, alanine aminotransferase; ApoA-I, apolipoprotein A-I; apoB, apolipoprotein B; ARMS, amplification refractory mutation system; AST, aspartate aminotransferase; BMI, body mass index; CACS, Coronary Artery Calcium Score; CCS, coronary calcium score; CHD, coronary heart disease; CIMT, carotid intima-media thickness; CK, creatine kinase; CRP, C-reactive protein; CTCAs, computerised tomography coronary angiography; CUS, carotid ultrasonography; CVD, cardiovascular disease; DLCNS, Dutch Lipid Clinic Network Score; EBESA, exon by exon sequence analysis; ECG, electrocardiography; EST, exercise stress test; FH, familial hypercholesterolaemia; FMD, flow-mediated dilatation; FDA, Food and Drug Administration; GP, general practitioner; HDL, high density lipoprotein; InterChol, International Cholesterol Foundation; LDL, low density lipoprotein; LFT, liver function test; Lp(a), lipoprotein(a); MBS, Medicare Benefits Schedule; MEDPED, Make Early Diagnosis to Prevent Early Deaths; MLPA, Multiplex Ligation Probe Amplification; MoC, model of care; NATA, National Association of Testing Authorities; NHMRC, National Health and Medical Research Council; NPAAC, National Pathology Accreditation Advisory Council; PBS, Pharmaceutical Benefits Scheme; PCSK9, proprotein convertase subtilisin/kexin type 9; PGD, pre-implantation genetic diagnosis; PND, prenatal diagnosis; RCPA, Royal College of Pathologists of Australasia; SHAPE, Screening for Heart Attack Prevention and Education Task Force; TGA, Therapeutic Goods Administration; TSH, thyroid-stimulating hormone.

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Keywords: Familial hypercholesterolaemia; model of care; adults; children; adolescents; diagnosis; genetic testing; cascade screening; assessment; treatment
1. Introduction

Familial hypercholesterolaemia (FH) is the most common and serious form of inherited hyperlipidaemia [1]. FH is due to dominant mutations of genes predominantly affecting the function of the low-density lipoprotein (LDL) receptor that clears LDL particles from plasma [2,3], and hence results in marked elevation in plasma LDL-cholesterol concentration. FH is present from birth and accelerates the onset of all forms of atherosclerotic cardiovascular disease (CVD), especially coronary heart disease (CHD), by one to four decades [1,4,5]. Opportunistic diagnosis of FH followed by screening of family members, the so-called cascade screening, can detect individuals at an early stage of FH [4,6–11]. This is critically important because it enables early intervention including lifestyle measures, cholesterol-lowering medica-
Table 1
Grades for recommendations employed for consensus statements.

<table>
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<th>Grade of recommendation</th>
<th>Description</th>
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<tr>
<td>A</td>
<td>Recommendation can be trusted to guide practice</td>
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<tr>
<td>B</td>
<td>Recommendation can be trusted to guide practice in most situations</td>
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<tr>
<td>C</td>
<td>Recommendations may be used to guide practice, but care should be taken in its application</td>
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These grades were applied to each of the recommendations in Section 2. Individual members of the Steering Committee were asked to grade the recommendations based on their knowledge of the literature and what they considered best practice in caring for patients with FH. Gradings were discussed and after full consensus of the committee was reached a final grade was ascribed to each recommendation. All members of the FH Australasia Network Consensus Group approved the final gradings.

The MoC is intended primarily for lipid disorder clinics in tertiary centres intending to initiate or develop a clinical service for FH. The MoC has been informed by published research, clinical experience, expert opinion and international guidelines for managing FH [5,12–16,30–34]. The major premises for these recommendations were published data on clinical efficacy and outcomes, but information on cost-effectiveness was also employed where available. Expert opinion was sourced from diverse stakeholders from the disciplines of adult medicine, paediatric and adolescent medicine, clinical genetics, clinical biochemistry, nursing, pharmacy, general practice, population health, and health economics; a patient support group was also consulted. The MoC significantly extends and consolidates other Australian recommendations on the detection and management of FH [10,15,32,35–38].

The MoC is presented as a series of recommendations (Table 1, Section 2) and algorithms (Fig. 1) that if followed could provide a cost-effective, standardised system of care likely to have the highest impact on patient outcomes. The recommendations were graded according to a modified NHMRC classification [39], and reflected the full consensus of an expert committee that was based on knowledge of the relevant literature and best clinical practice. Algorithms were chosen to provide easy visualisation of the concepts underpinning the MoC. The algorithms are accompanied by background information and explanatory text and reflect the recommendations of the Consensus Group. This MoC should not be perceived as prescriptive, but as a tool for guidance. It should therefore be complemented by good clinical judgment and adjustments made to the model according to local requirements, protocols and resources. Acknowledging the lack of objective evidence supporting its clinical-efficacy and cost-effectiveness, this MoC for FH should be viewed as an evolving set of diagnostic and care pathways that will need periodic review, clinical appraisal and modification.

Fig. 1. Overview of algorithms for model of care for FH.
## 2. Summary of recommendations

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<th>Recommendation I</th>
<th>Models of care and components of service</th>
<th>Grade</th>
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<tr>
<td>Figs. 1 and 12</td>
<td>a. Models of care for familial hypercholesterolaemia (FH) should focus on detecting, diagnosing, assessing and managing index cases, as well as on risk notification and cascade screening of family members.</td>
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<td></td>
<td>b. Adults and children/adolescents will require different models of care.</td>
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<td>c. All services need to be integrated across several specialties and incorporated into primary care.</td>
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<td>d. Good clinical governance, teaching and training programs, and family support groups are integral to all models of care.</td>
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<th>Recommendation II</th>
<th>Identifying index cases</th>
<th>Grade</th>
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<tr>
<td>Fig. 2</td>
<td>a. Index cases of FH should be sought amongst adults with premature cardiovascular disease in primary and secondary care settings.</td>
<td>A</td>
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<td>b. In adults a simple clinical tool based on the Dutch Lipid Clinic Network Score should be used.</td>
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<td>c. All patients with possible-to-definite FH should be referred to a lipid disorders clinic for more detailed assessment and institution of cascade screening.</td>
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<th>Recommendation III</th>
<th>Clinical assessment and management allocation of adults</th>
<th>Grade</th>
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<td>Fig. 3</td>
<td>a. Secondary causes of hypercholesterolaemia should first be excluded.</td>
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<td>b. The diagnosis of FH should be made using both phenotypic and genetic testing.</td>
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<td>c. Patients should be stratified into risk categories according to presence of cardiovascular risk factors and personal history of cardiovascular disease.</td>
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<td>d. Risk stratification should guide the intensity of medical management.</td>
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<th>Clinical assessment and management allocation of children and adolescents</th>
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<td>Fig. 4</td>
<td>a. Children (≥ 5 yr) and adolescents should be tested for FH after the diagnosis of FH has been made in a parent.</td>
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<td>b. Secondary causes of hypercholesterolaemia should first be excluded.</td>
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<td>c. With rare exceptions, children and adolescents should only be genetically tested for FH after a pathogenic variant (mutation) has been identified in a parent or first degree relative.</td>
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<td>d. Age- and gender-specific plasma LDL-cholesterol concentration thresholds should be used to make the phenotypic diagnosis of FH, an LDL-cholesterol ≥ 5.0 mmol/L indicating highly probable/definite FH; two fasting lipid profiles are recommended.</td>
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<td>e. Patients should be stratified into risk categories according to age, presence of other cardiovascular risk factors, prematurity of family history of cardiovascular disease and the level of hypercholesterolaemia at diagnosis.</td>
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<td>f. Risk stratification should guide the intensity of medical management.</td>
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<th>Management of FH in adults</th>
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<td>Fig. 5</td>
<td>a. All adult patients with FH must receive advice on lifestyle modifications and all non-lipid risk factors must be addressed.</td>
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<td>b. Plasma LDL-cholesterol targets for routine, enhanced and intensive management should be &lt;4 mmol/L, &lt;3 mmol/L, &lt;2 mmol/L, respectively.</td>
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<td>c. Achieving these targets will require a fat-modified diet, plant sterols (or stanols) and a statin with or without ezetimibe.</td>
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<td>d. Niacin, resins and a fibrate may be required with more intensive strategies.</td>
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<td>e. Plasma levels of hepatic aminotransferases, creatine kinase and creatinine should be measured before starting pharmacotherapy. All patients on pharmacotherapy, particularly statins, should have hepatic aminotransferases monitored; creatine kinase should only be measured when musculoskeletal symptoms are reported; creatinine should be monitored in those with kidney disease.</td>
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<td>f. All women with FH of child-bearing age should have pre-pregnancy counselling</td>
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<td>g. Statins and other systemically absorbed lipid regulating agents should be discontinued 3 months before conception and during pregnancy and breast feeding in women with FH.</td>
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<td>h. Non-invasive testing for coronary heart disease and atherosclerosis should be considered in patients undergoing standard and enhanced treatment, with a step-up in treatment considered if there is evidence of progression of disease. Non-invasive testing for atherosclerosis need not be carried out more frequently than every two years.</td>
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<td>i. Patients receiving standard or enhanced management should be reviewed every 6–12 months, and those receiving intensive management should be reviewed according to clinical context, with appropriate interval assessment of cardiac function and referral to cardiology.</td>
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**Recommendation VI**

**Management of FH in children and adolescents**

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**Fig. 6**

a. Patients must receive advice on lifestyle modifications and non-lipid risk factors must be addressed. Effective anti-smoking advice is mandatory.
b. Lowest risk patients should be treated expectantly with a fat-modified diet with or without plant sterols (or stanols), with statins considered after the age of 10 years in boys and after the menarche in girls.
c. Plasma LDL-cholesterol targets for intermediate and high risk patients should be <4 mmol/L and <3 mmol/L, respectively.
d. Reaching these targets requires a fat-modified diet, plant sterols (or stanols) and a statin with or without ezetimibe or a bile acid sequestrant.
e. The preferred statins for initiating therapy are those that are licensed for clinical use in this age group; in Australia these are pravastatin, fluvastatin or simvastatin, but other statins may be prescribed according to clinical indications.
f. Weight, growth, physical and sexual development, and well-being should be reviewed regularly in all patients.
g. Plasma levels of hepatic aminotransferases, creatine kinase and creatinine should be measured before starting pharmacotherapy. All patients receiving statins should have hepatic aminotransferases monitored; creatine kinase should be measured when musculoskeletal symptoms are reported; creatinine should be monitored in those with kidney disease.
h. Carotid artery ultrasonography should be considered for assessing intima-medial thickness and presence and progression of plaques; this may guide the intensity of medical management.

**Recommendation VII**

**LDL-apheresis for FH**

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**Fig. 7**

a. LDL-apheresis should be considered in patients with homozygous or compound heterozygous FH.
b. LDL-apheresis should be considered in patients with heterozygous FH with documented coronary heart disease who are refractory to or cannot tolerate cholesterol lowering medication.
c. LDL-apheresis should be considered in children with homozygous or compound heterozygous FH by the age of 5 years, particularly if the plasma cholesterol concentration remains at 9 mmol/L or above on medication.
d. LDL-apheresis should be carried out in close collaboration with a centre experienced in apheresis, such as a transfusion medicine service.
e. The efficacy, tolerability and safety of LDL-apheresis must be reviewed after each treatment.
f. The effect of LDL-apheresis on progression of atherosclerosis should be monitored with echocardiography (aortic valve and root), carotid ultrasonography and/or exercise stress testing.

**Recommendation VIII**

**Cascade screening: risk notification and genetic/phenotypic testing of families**

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**Figs. 8 and 9**

a. Notification of relatives at risk of FH should not be instigated without the consent of the index case, with the exception noted below in recommendation c).
b. If no consent is given by the index case, rapport should continue to be built and consideration given to referral for counselling.
c. Relatives should only be directly notified of their risk without consent of the index case if there is specific legislative provision for this breach of confidentiality in the relevant jurisdiction.
d. Commonwealth legislation, local state legislation, NHMRC guidelines and local health service protocols about disclosure of medical information without consent should be consulted.
e. A proactive approach that respects the principles of privacy and autonomy is required.
f. All material sent to relatives and the telephone approach should be clear, comprehensible and not cause alarm. General and specific modes of communication should be used.
g. Cascade screening should ideally be carried out as a formal collaborative process between lipid disorders and clinical genetics services. It should also involve close communication and liaison with primary care physicians and employ a user-friendly family based data management system.
h. Pre-testing counselling should be offered to at risk family members of an index case prior to phenotypic or genetic testing.
i. If no consent/assent for genetic testing is obtained phenotypic testing for FH should be offered.
j. If genetic testing detects the family mutation, a definitive diagnosis of FH can be made in the tested individual particularly when the phenotype also suggests FH.
k. If genetic testing does not detect the family mutation, the diagnosis of FH can be excluded, except when the clinical phenotype is highly suggestive of FH.
3. Overview of algorithms for the model of care

Fig. 1 provides an overview for the MoC for FH. The sequence of presentation is as follows: detection of index cases and clinical diagnostic criteria (Fig. 2; Appendices 2–4); diagnosis and assessment of adults, children and adolescents (Figs. 2–4); management of FH in adults, children and adolescents (Figs. 5 and 6); LDL-apheresis and radical therapy for FH (Fig. 7); cascade screening, including risk notification and predictive testing (Fig. 8); clinical and laboratory protocols for genetic testing (Figs. 9–11); optimal components of a clinical service for FH (Fig. 12). The MoC has initially been devised for use within a specialised setting, such as a lipid clinic, run out of departments of internal medicine, cardiology or endocrinology in secondary or tertiary referral centres. The MoC will need to be further developed to consider current and future potential roles for primary care providers.

4. Detection of index cases and diagnosis of FH

A key challenge facing the care of FH is the systematic detection of index cases [37,38,40]. The term ‘index case’ refers to the first individual diagnosed with FH in the family. Identifying index cases is important because it represents the starting point for family tracing, referred to as ‘cascade screening’, by which the majority of FH cases can be efficiently detected [4,7–9,11]. There are several diagnostic tools for diagnosing FH clinically, including those from the Dutch Lipid Clinic Network [34], Simon Broome Registry [12,41] and the US MEDPED Program [42] (see tables in Appendices 2–4, respectively). There are, however, no internationally agreed criteria for the phenotypic diagnosis of FH [8,37,43]. We favour the Dutch Lipid Clinic Network Score (DLCNS) because we consider it simpler for clinical use and the numerically integrated scoring system [34,37], which does not fully rely on the plasma level of LDL-cholesterol, can provide a more sensitive method for detecting index cases with FH [8,44]. The Simon Broome system is an alternative tool favoured in the UK [12] that is comparable to the DLCNS in predicting an FH mutation, [8] but could overlook patients with true FH who may not be overtly hypercholesterolaemic. The MEDPED System, which is based solely on plasma total and LDL-cholesterol and has some practical appeal, is less sensitive than the other criteria in predicting an FH mutation and accurate implementation requires that cholesterol measurements be widely known in family members [42,45]. Illustrative examples of the typical examination features (arcus cornealis, tendon xanthomata) of FH are given in Appendix 5. Gender- and age-specific thresholds for plasma LDL-cholesterol for diagnosing first-degree relatives with FH were recently published [46], but their value in clinical practice has not yet been reported. The phenotypic diagnosis of FH should be based on at least two fasting measures of plasma LDL-cholesterol [14,47–49]. The value of taking a family history of CHD is well established [5,12,14–16,33,34,50], but its use is often neglected in clinical practice [22,51] and this needs rectification [52–54]. Secondary causes of hypercholesterolaemia (e.g. primary hypothyroidism, proteinuria, cholestasis, and medications such as corticosteroids) must also be excluded [14,15], but it is important to note that FH may co-exist with other cardiovascular risk factors [55–57], most importantly metabolic syndrome and diabetes [17a]. LDL-cholesterol is underestimated by the Friedewald equation at plasma triglycerides >4.5 mmol/L [47], above which a well validated, direct assay should be employed to measure LDL-cholesterol.
Fig. 2 indicates that potential index cases of FH should be sought amongst patients aged less than 60 years with CVD presenting to coronary care, stroke, cardiothoracic and vascular units [43], as well as amongst similar patients attending cardiac rehabilitation programs. The greatest yield will be from screening younger adult patients with CHD [22,38,41,60]. Where the suspicion of FH is high, preliminary assessment of patients using either a full or modified DLCNS should be employed [22,34]. A simplified modification of the DLCNS, suitable for use by non-specialists, involves estimating a score for family and personal clinical history and LDL-cholesterol alone [22,37]; for patients on statins an upwards adjustment of approximately 30% in LDL-cholesterol could be employed [61] if the pre-treatment LDL-cholesterol is unknown. The role of this simple tool requires evaluation. A persuasive case for universal, as opposed to selective, screening of children for hypercholesterolaemia has been made, since deficiency in obtaining a family history of CHD and/or hypercholesterolaemia will result in children not being tested and treated for FH [62]. It has been proposed that this could be done at immunization using plasma cholesterol alone and subsequent child–parent testing where indicated [63] or by universally screening children aged 9–11 years with a standard lipid profile [64a]. However, the acceptability, specificity and cost-effectiveness of these universal screening strategies for FH are questionable [4,65,66].

Opportunistic application of the DLCNS should also be employed in specialist clinics and in primary care. General practitioners (GPs) are usually the first to encounter individuals who may have unsuspected FH in the community, and are therefore critically placed for detecting index cases [12,67,68]. Planned health assessment in middle age, such as the 45–49 year old health check assessment (Medicare Benefits Schedule (MBS) Item A27) [69] would be an opportune time for GPs to routinely test for FH, but its uptake and yield needs evaluation. Children with a positive family history of hypercholesterolaemia or premature CHD should be screened for FH [64a], but this is best done as part of a co-ordinated cascade testing process [9,12]. In primary care a retrospective search of clinical databases affords another opportunity for generating new cases of FH [67]. Flagging of laboratory reports on patients with plasma cholesterol concentrations >7 mmol/L is another method for alerting practitioners about the possibility of FH, but its yield and cost-effectiveness remain to be reported. There is also a role for opportunistic application of the DLCNS by community pharmacists to patients attending to collect a prescription for a statin [70], with the possibility of on-site testing of relatives with a finger prick cholesterol measurement. Another opportunity for detecting FH is amongst patients referred to rheumatologists with tenosynovitis or to plastic surgeons for the excision of tendon masses. Certain ethnic groups in the community, such as Christian Lebanese, Afrikaanders and Lithuanian Jews, in whom the prevalence of FH is particularly high due to a gene founder effect [1], should also be targeted for screening for the condition; culturally appropriate processes should be followed.

When the DLCNS is ≥ 3, we recommend referral to a specialised FH service or lipid clinic for confirmation of the diagnosis and advice on management and cascade screening. Health providers working in these clinics should have competence and training in both clinical lipidology and prevention of CVD [26,71,72]. FH is unlikely when the DLCNS is <3 [8,44]. This needs to be appropriately communicated to the patient and their GP. For patients on statins, or other cholesterol lowering medications, a contemporary plasma LDL-cholesterol concentration will give a falsely low DLCNS and pre-treatment values must be obtained to accurately assess the chance of having FH. Hence, we recommend that index cases of FH should be identified in a two-stage process starting with initial phenotypic assessment using the DLCNS followed by referral to a specialist FH service. Employing a DLCNS as low as 3 as a criterion for referring patients to a lipid clinic may be too sensitive [8,38], in which case the score may be increased according to workloads and resources. If resources allow, an alternative approach would be to genetically screen for FH in all patients with premature CHD (e.g. age <50 years) presenting to the cardiac services referred to in Fig. 2. All patients identified as having a likelihood of FH should be provided with simple and clearly written information explaining the importance of FH and the steps involved in diagnosing the condition in them and their relatives [8,12,37]. The recommended protocols for risk notification and cascade screening of relatives and for genetic testing are discussed later and given in the algorithms in Figs. 8–10.

5. Assessment of adult patients

Whether classified as having possible, probable or definite FH [34], all patients should have a detailed clinical assessment to investigate other cardiovascular risk factors, presence of symptomatic or subclinical atherosclerosis and secondary causes of hypercholesterolaemia. Clinical assessment should ideally be undertaken by a specialist trained in clinical lipidology [26,71], with skills in preventative cardiovascular medicine [72]. The risk of CVD amongst patients with FH can vary widely [43,73]. This may relate to the pre-treatment plasma level of cholesterol, genetic causes affecting lipid metabolism or arterial biology, and the presence of other major cardiovascular risk factors, in particular smoking, obesity, hypertension and diabetes [43,55–57,74]. Pathogenic genetic variants (mutations) that lead to very elevated plasma cholesterol and premature CHD may also be considered a major risk factor [66], as should an elevation in plasma lipoprotein(a) (Lp(a)) concentration >0.5 g/L [75].
Box 1, linked to Fig. 3, gives mandatory, and recommended (but optional) clinical indices that may be useful in assessing patients with FH. Non-invasive tests for atherosclerosis and CHD should be considered optional and individualised to specific clinical situations [76–78], being particularly useful in FH when the family history of CVD is unclear [79]. Carotid ultrasonography (CUS) can be a particularly useful test that recognizes that in FH atherosclerosis is also accelerated in extra-cranial cerebral arteries and its detection serves as a surrogate for the involvement of coronary arteries [80–82]. Clinical assessment must take account of the psychological, intellectual, social and ethnic status of the patient [8,83–86], and potential need for special methods of counselling. Inadequate health literacy is not uncommon and must be addressed [87,88]. Detailed exploration and clear communication and discussion of the individual’s family history of CVD are essential for effective management of FH [89,90]. After clinical assessment, patients should be divided into those at lowest, intermediate and highest risk of CVD; categories should be modified according to regular clinical review (see Fig. 5).

This stratification of patients is consistent with other approaches to cardiovascular risk assessment [14–17a]. At lowest risk are patients with no other cardiovascular risk factors (smoking, obesity, diabetes, and hypertension) and negative tests for subclinical atherosclerosis. At intermediate risk are patients with at least one other cardiovascular risk factor or subclinical evidence of early atherosclerosis. At highest risk are patients with a history of symptomatic CVD (coronary, cerebral or peripheral vascular disease) and/or a revascularization procedure, or with subclinical evidence of more advanced atherosclerosis. Subclinical atherosclerosis may be defined according to published guidelines [77,78] – no evidence: a carotid intima-medial thickness (CIMT) < 75th percentile (for age and sex) with no carotid plaques or a Coronary Artery Calcium Score (CACS) of zero; early evidence: a CIMT > 75th percentile with no plaques (or stenosis) or a CACS ≥ 1 but <100; more advanced evidence: presence of carotid plaques (or stenosis) or a CACS > 100. If electing to do ankle brachial index (ABI), exercise electrocardiography (ECG) testing and/or computerised tomography coronary angiography (CTCA) in asymptomatic patients on clinical grounds, abnormal results by recognised criteria [13,77,78,91] may also be employed in allocating patients to the higher risk categories shown in Fig. 3.

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Potential sources for identifying index cases with FH:
- Coronary Care
- Cardiac Rehabilitation
- Cardiothoracic Surgery
- Stroke Unit
- Vascular Surgery
- Ward nursing staff
- Specialists
- GPs
- Laboratory report alerts
- Pharmacists
- Clinical Genetics Services
- Opportunistically in clinics/hospitals

High index of suspicion for new cases, Retrospective audit for previous cases, Use simplified modification of phenotypic criteria for FH (Appendix 2 & 3)

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**Fig. 2. Detection of index cases and diagnosis of FH.**
Box 1: Information used for clinical assessment of adults with FH

- **Mandatory**: Age, gender, history: CVD (coronary, cerebral and peripheral arterial disease)/revascularisation, history of major cardiovascular risk factors, psychological and socioeconomic status, family history of hypercholesterolaemia and CVD, BMI, waist circumference, blood pressure, bruits, arcus cornealis, xanthelasma, tendon xanthomata, triglycerides, total cholesterol, HDL-C, Lp(a), apoB, smoking status, menopausal status, reproductive status, drug history

- **Recommended/optional**: glucose, insulin, CRP, creatinine, TSH, albuminuria, ApoA-I, ABI, EST, carotid and Achilles tendon ultrasound, CTCA/calcium score

- **Major CVD Risk factors** include very elevated LDL-C (>7 mmol/l), low HDL-C, diabetes, smoking, obesity, hypertension, high Lp(a), family history of very premature CHD.

Fig. 3. Assessment of adult patients.

This subdivision into lowest, intermediate and highest risk allows management to be classified as standard, enhanced and intensive, respectively. This risk stratification procedure will allow the best use of clinical resources, which can in turn increase cost-effectiveness. Framingham risk scores, or scores derived from other cardiovascular risk engines, are not sufficiently reliable to guide management in FH [14,15,38], particularly in younger patients, in whom a measure of long-term risk based on imaging of subclinical atherosclerosis may be more appropriate [92]. Another option would be to offer intensive management to intermediate and highest risk cases of probable/definite FH. Similarly, enhanced management could be considered for the lowest risk cases with probable/definite FH and for the possible cases of FH who are at intermediate or highest risk of CVD. The yield and cost-effectiveness of all these different therapeutic strategies requires further evaluation. The importance of assessing other cardiovascular risk factors beyond hypercholesterolaemia is particularly underscored by the rising tide of obesity, type 2 diabetes and hypertension in our community [17a,93,94]. Patients considered to have a homozygous FH phenotype should evidently be classified at exceptionally high risk [43,95] and be referred for consideration for radical therapy using LDL-apheresis (see Fig. 7).

6. Diagnosis and assessment of children and adolescents

One of the most potentially contentious issues in the care of FH is the identification of the condition in children and adolescents [48,96–100]. Efforts are well justified by clear indications that FH remains underdiagnosed particularly in the young [18,21,96] and that untreated patients suffer cardiovascular damage from an early age [81,96,101,102]. Furthermore, there are reassuring data concerning the safety and efficacy of dietary and pharmacological treatments [99,103–108], including confirmation that children receiving statins achieve normal growth and developmental milestones and do not exhibit alterations in plasma adrenocortical hormone levels. While there have been concerns about the psychological impact of ‘disease labelling’ from an early age [8,84,85], formal studies provide reassurance that this is not a significant issue [7,86,109]. Despite advances in the overall care of patients with FH, medical services for children with the condition remain particularly underdeveloped [110].

Fig. 4 summarizes the recommended approaches to the diagnosis, assessment (Box 2), and risk stratification allocation of FH in children and adolescents. We recommend that FH screening be offered to all children (aged ≥ 5 years) and adolescents at risk of having FH, particularly in the context of a co-ordinated cascade testing process. Other recommendations suggest screening at risk children earlier at ≥2 years of age [64a,b] and universally screening all children for dyslipidaemias aged 9–11 years [64a]. Under the age of 5 years screening may be justified where there is a strong desire from the parents or severe FH (homozygous or compound heterozygous) is suspected, consistent with other guidelines [12,98]. Because the DLCNS is not applicable to children, the diagnosis of FH must rely either on serial measurements of a fasting plasma level of LDL-cholesterol [46,48,97], or
preferably on genetic testing where a recognised mutation for FH has been detected in a parent [7,8,66]. Secondary causes of hypercholesterolaemia must be excluded [64a,b]. Irrespective of whether the diagnosis of FH will be made genetically, plasma LDL-cholesterol must be measured in all patients since the result is essential to guide therapy [96–98]. Predictive genetic testing of children for FH is also well justified as preventive treatment can be instituted before adulthood with lifestyle measures and pharmacotherapy [96–98,103,108] (see Fig. 4). Genetic counselling including discussion of the implications of DNA testing in children should be provided at the time the parent receives the genetic results confirming the diagnosis of FH [8,85,111–115]. Because of ethical issues involved in genetically testing minors [114,115], it is usual and best practice to first genetically test a phenotypically affected parent [64b]. This can also circumvent issues related to a non-paternity event. In rare circumstances, such as refusal of a parent to be tested first or when autosomal recessive FH is suspected [3], genetic testing may first be carried out in the child. Another special situation may arise when the child has significant hypercholesterolaemia without the detection of the family’s pathogenic mutation. In this case, after exclusion of secondary causes of hypercholesterolaemia and appropriate genetic counselling, other causative mutations for FH should be sought from the extended pedigree. Detecting an FH causing mutation would make the child or adolescent eligible for Pharmaceutical Benefits Scheme (PBS) government subsidy for a statin at an LDL-cholesterol > 4.0 mmol/L when the family history of premature CVD or tendon xanthomata is unclear or unobtainable [116]. When an FH causing mutation is unknown in the parent, the diagnosis of FH in children should be based on age and sex adjusted LDL-cholesterol levels, the 95th percentile being 3.5 mmol/L for boys and 3.8 mmol/L for girls [37,48] (see Fig. 4). If employing the modified Simon Broome Criteria, the universal cut-off for probable FH is LDL-cholesterol > 4.0 mmol/L [12,41]. At least two consecutive measurements of LDL-cholesterol over 6 months in fasting samples should be used to make the phenotypic diagnosis of FH [49,98]; a non-fasting lipid profile may be employed as an initial screening test, however. Knowledge of the child’s plasma LDL-cholesterol and whether a parent is being treated with a statin may provide a simple clinical tool for diagnosing FH [117]. Most children with plasma LDL-cholesterol >95th percentile for age and sex and an autosomal dominant pattern for inherited hypercholesterolaemia, in whom secondary causes of dyslipidaemia have been excluded, will have an FH causing mutation [118]. The thresholds for plasma LDL-cholesterol concentration recommended above for making a phenotypic diagnosis of FH are compatible with those recently reported to accurately predict an FH causing mutation [46]. Whether using phenotypic or genetic approaches, screening children for FH requires expertise in working with and giving advice to families [8,84,98,119,120] and is best undertaken in close liaison with paediatric services and where indicated with genetic counsellors [115,121].

![Diagram of diagnosis and assessment of children and adolescents.

**Box 2: Information used for clinical assessment of children and adolescents with FH**

**Mandatory:** Age, gender, history including cardiovascular risk factors, psychological status, family history of hypercholesterolaemia and CVD, BMI, waist circumference, blood pressure, bruits, arcus cornealis, xanthelasma, tendon xanthomata, triglycerides, total cholesterol, LDL-C, HDL-C, Lp(a), apoB, smoking status, reproductive status, drug history

**Recommended/optional:** glucose, insulin, CRP, creatinine, TSH, albuminuria, ApoA-I, CUS for early atherosclerosis, FMD of brachial artery for endothelial function.

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**Fig. 4. Diagnosis and assessment of children and adolescents.** See text for caveats.
All individuals with at least a possible diagnosis of FH should be clinically assessed according to mandatory and recommended (but optional) requirements shown in Fig. 4. With few exceptions, these are generally similar to those recommended previously for adults. Of the available non-invasive tests for subclinical atherosclerosis in children and adolescents, measurement of CIMT with ultrasonography is the most promising at present, but it requires special expertise and if used in risk stratification should be carried out according to recommended protocols [82,122]. With the exception of homozygous or compound heterozygous FH, boys aged less than 10 years and girls who have not reached the menarche should generally be considered to have low risk FH and receive expectant treatment. Boys over the age of 10 years and girls who have reached the menarche without cardiovascular risk factors or objective evidence of increased CIMT should be considered to have moderate risk FH and receive enhanced treatment. Boys over 10 years and girls who have reached the menarche, with a family history of very premature CVD, two or more major cardiovascular risk factors, or LDL-cholesterol > 6 mmol/L, should be considered to have high risk FH and receive intensive treatment [12,96–98]. Certain high-risk children and adolescents with FH should ideally be managed in a joint adult- paediatric FH clinic [123]. Factors that may be used to triage patients for this clinic include family dynamics, current lifestyle of the family and child, adherence to treatment, severity of family history of CHD, and presence of other major cardiovascular risk factors (obesity, hypertension, diabetes and smoking) [123,124]. While all children with FH should ideally be referred to a paediatric service, we consider it feasible for affected parents and children to be reviewed together by an adult service in a ‘family clinic’ [123], provided staff have the required competencies and the environment of the clinic is appropriate. Young FH patients being reviewed in a paediatric clinic should be referred to an adult clinic around the age of 16 years, with appropriate arrangements made for transitional care and with close involvement of the GP.

7. Management of adults

Fig. 5 shows the protocols for adult patients with FH allocated to standard, enhanced and intensive management. In parallel with lowering elevated plasma cholesterol, appropriate lifestyle modifications should be emphasised and all major non-lipid cardiovascular risk factors must be treated according to expert guidelines [14,16,17a,32,33,125–129]; offering advice and support on smoking cessation is mandatory. Low-dose aspirin should be used in highest risk FH and considered in intermediate risk FH [128].

7.1. LDL-cholesterol and apoB targets

The recommended therapeutic targets for absolute plasma concentrations of LDL-cholesterol and apolipoprotein B (apoB) are given in Fig. 5. These targets have been chosen to be compatible with other therapeutic guidelines for the management of hypercholesterolaemia [13–16,32,59]; therapeutic targets should evidently be lower with increasing CVD risk. Measuring apoB may not, however, be necessary in leaner FH patients with plasma triglyceride concentrations <2.0 mmol/L. ApoB accurately reflects the plasma concentration of atherogenic LDL particles. ApoB is particularly useful, and preferable to LDL-cholesterol, when LDL particle number increases and both size and density fall as a consequence of hypertriglyceridaemia [58,59].

Hypertriglyceridaemia is a feature of obesity, metabolic syndrome and type 2 diabetes [17a], all of which are increasing in prevalence in the background population and hence amongst patients with FH [93,94]. Use of an apoB target may be restricted to FH patients who exhibit an elevated triglyceride level > 2.0 mmol/L [17a,58]. Even with contemporary treatments, achieving the absolute targets for LDL-cholesterol and apoB shown in Fig. 5 may not be attainable by some patients, particularly those with a higher baseline plasma cholesterol [61], in which case a more realistic general target of a 40–50% reduction from pre-treatment levels could be used [12,128].

7.2. Diet and lifestyle modifications

Diet and lifestyle modifications are cornerstones of the management of all types of dyslipidaemias [14–17a,32,33,59,130], including FH [13,131]. Diets should be low in saturated fat and energy and adjusted to achieve desirable body weight [15,132]. Dietary counselling by a registered dietician is recommended for all affected individuals and families [133]. Dietary supplementation with plant sterols or stanols should be considered [134]. Moderate intensity aerobic exercise for at least 30 min on 5 days of the week should be considered to prevent obesity and diabetes, with advice appropriately adjusted in those with established CHD [32]. Several strategies may be employed, where indicated and feasible, for improving long-term adherence to dietary and life-style changes, including involving the patient, setting goals, encouraging self-monitoring, frequent and prolonged contact, and motivational interviewing [135]. However, almost all patients will require medication to lower the elevation in LDL-cholesterol. Offering effective treatments and advice on smoking cessation is mandatory and appropriate management guidelines should be followed [32]. Alcohol consumption should be limited to no more than 2 standard drinks per day. Stress, anxiety and depression must be considered in all patients and managed accordingly [32,136].

7.3. Pharmacotherapy

In Australia, the PBS eligibility criteria for government subsidy for lipid modifying agents cover almost all adult patients with FH, particularly if the molecular diagnosis of
FH has been confirmed with a DNA test [116]. In New Zealand government subsidies are similar, but the spectrum of drugs is slightly more restricted [137]. HMG CoA reductase inhibitors (or statins) are by far the most common and effective drugs to treat FH [104,107,128,129,138–146]. Statins decrease the incidence of CHD [143–145] and are estimated to be cost-effective in treating FH [147,148]. Reduction in the costs of statins will, however, make the medical care for FH even more cost-effective in the future. All the major statins are government subsidised in Australia, but only atorvastatin, simvastatin and pravastatin are subsidised in New Zealand. After initiation of statin therapy, all patients should be reviewed at 6–8 weeks to monitor LDL-cholesterol response, adherence, safety parameters and tolerability [61], and 6–12 monthly thereafter if targets are achieved and no problems documented. The statin should be up-titrated to the maximally recommended tolerable dose that achieves the therapeutic targets shown in Fig. 5; patients may require switching to more potent statins [61], such as atorvastatin or rosuvastatin. Higher risk patients who require greater lowering of plasma LDL-cholesterol and apoB will require other drugs, especially ezetimibe [149,150], but also niacin, fenofibrate and bile acid binding resins [151–154]. Patients with higher plasma LDL-cholesterol levels will require a combination of drugs to achieve therapeutic targets. Combination drug regimens that target LDL-cholesterol can decrease progression of CHD in patients with FH [155]. Niacin may be particularly indicated for lowering high plasma Lp(a) concentration [75,151,152]; in FH we recommend an Lp(a) < 0.5 g/L [75]. Fibrates would be relatively contraindicated with a history of untreated cholelithiasis [156]. For patients not achieving treatment targets, additional agents should generally only be introduced after at least 12 months of testing and adjusting the statin regimen and confirming adherence to medication. In higher risk patients, additional agents should be considered after an earlier interval (e.g. 4–6 months) of testing the statin regimen. Residual hypertriglyceridaemia and low HDL-cholesterol (the so-called ‘atherogenic lipid profile’) while on a statin is an indication for considering treatment with niacin, a fibrate or higher doses of supplemental omega-3 fatty acid ethyl esters [152,157]. Hypertriglyceridaemia in FH patients should be managed according to recently published guidelines [158,159]. There is outcome evidence supporting use of lower doses of omega-3 fatty acids in patients who have sustained a myocardial infarction [160]. Niacin, fibrates and omega-3 fatty acid ethyl esters, together with a very low fat diet, will also be indicated in rare instances of severe hypertriglyceridaemia.
to prevent acute pancreatitis [14,157,161]. There has been renewed interest from Japan in the therapeutic role of probucol [162], a drug formerly used to treat FH and withdrawn from the European and US markets because of safety concerns; use of the present formulation of this drug cannot be recommended.

7.3.1. Safety monitoring

Plasma hepatic aminotransferases (ALT, AST), creatine kinase (CK) and creatinine levels should be measured routinely as baseline safety checks prior to starting medications [61,163]. Hepatic aminotransferases should be monitored according to the approved product information for the drugs, and checked at least every 3 months if there is a history of liver disease (e.g. chronic hepatitis or cirrhosis) or more frequently if plasma levels rise to three-fold greater than the upper reference limit; measurement of serum bilirubin may also be used to indicate the severity of liver toxicity. Plasma CK should be measured when musculoskeletal symptoms are reported. Particular vigilance is required in patients receiving higher doses of a statin, and patients predisposed to statin side-effects, specifically the elderly and those taking multiple medications including the combination of a statin with a fibrate [163,164]. Patients on niacin also require monitoring of plasma glucose and uric acid because of a small, but significantly increased risk of hyperglycaemia and hyperuricaemia [165]. Plasma ALT and AST should be measured about every 6 months in patients receiving statin–niacin and statin–fibrate combinations. Evidence of chronic kidney disease, as estimated by an elevation in plasma creatinine and fall in estimated glomerular filtration rate, would be a precautionary indication to initiate treatment with, or switch to, a statin that is not eliminated by the kidney [61]. Statins should not be initiated if the baseline plasma, ALT, AST or CK levels are >3 times the upper reference limit. Discontinuation of the statin or revision of the dose or regimen is required when the plasma aminotransferase or CK levels rise to >3 times the upper reference limit on treatment. Alternative agents such as an ezetimibe or bile acid sequestrants may need to be substituted for a statin.

7.3.2. Medication adherence and tolerance

Pharmacists could play a key role by monitoring patients’ use of therapy, flagging non-adherent patients to GPs and clinics, reducing therapeutic complexity and by more direct involvement in improving adherence to medication [166–169]. FH patients who are non-adherent to therapy are best reviewed in a dedicated clinic that could involve input from pharmacy, clinical pharmacology, psychology and nursing [170]. Action plan interventions may be more effective in FH than interventions aimed at altering perceptions about taking statins [171]. Detailed communication and discussion of an individual’s family history of CVD may improve adherence to treatment [89,90]. Health literacy must also be considered [172,173]. The underlying causes of hypercholesterolaemia and adherence to statin therapy remains a significant issue amongst many at risk patients who have not specifically been diagnosed with FH [174,175]. This also needs addressing at a primary care level in the community [176–178]. Poor control of hypercholesterolaemia and other risk factors for atherosclerosis is a particular on-going concern in all patients with CHD [179,180].

Patients who are intolerant of medications require special support and follow-up [170]. Musculoskeletal side-effects can be frequently reported with statins and require specialist care [170,181]. Potential drug interactions with statins should be closely monitored, [163] noting the increased risk with drugs that are metabolised by CYP3A4 with simvastatin and atorvastatin and by CYP2C9 with rosuvastatin and fluvastatin [61,163]. Ezetimibe is well tolerated and has a statin dose sparing effect [149,150]. Bile acid binding resins have frequent gastrointestinal side-effects (e.g. constipation and abdominal discomfort) and can affect the absorption of other drugs and fat soluble vitamins [153]; tolerability is greatest with colesevelam [182]. Resins should be taken with meals and gastrointestinal side-effects minimised by increasing fluid and fibre intake and use of stool softeners [153]. Flushing is a problem with niacin, but this is diminished with the newer formulations (Niacin-ER, Tredaptive) and co-administration of aspirin [151,152]; hyperglycaemia can be a particular problem in FH patients with impaired glucose tolerance or diabetes, and hyperuricaemia in those with a history of gout [165]. Co-administration of fibrates and a statin can increase the risk of myopathy, but this is diminished significantly when a statin is combined with fenofibrate [156,163].

7.4. Review intervals and shared care

Uncomplicated patients on routine therapy may be referred back to the GP for long-term follow-up, but should also be reviewed annually in a lipid disorders clinic. Those receiving enhanced care should also be monitored in the lipid clinic at 3–6 monthly intervals until plasma LDL-cholesterol targets are achieved and if stable should be reviewed annually in this clinic with 6 monthly follow-up by the GP. Patients receiving intensive management should be retained in the lipid disorders clinic and reviewed at intervals determined by clinical context and requirements. When changing medication and increasing doses, patients may need more frequent review. Systems for the shared care of FH patients between specialties and primary care need to be further investigated in order to appropriately inform future MoCs for FH [68].

7.5. Assessing atherosclerosis and CHD

CTCA, CUS, ankle-brachial index measurement, stress echocardiography, treadmill ECG and myocardial nuclear perfusion scanning are all potential options for monitoring subclinical atherosclerosis and/or symptomatic coronary disease [76–78] (see Fig. 5). Consistent with expert recommendations [76–78,91], we consider that there is potential
value in non-invasive testing in asymptomatic FH patients for atherosclerosis and coronary disease. However, non-invasive testing has been better validated for assessing target organ damage and stratifying risk than for monitoring progression of disease [13,79]. Nevertheless, clear evidence of progression of atherosclerosis in coronary, carotid or femoral arteries should be a clinical indication for intensifying treatment and attaining the recommended targets for LDL-cholesterol and apoB [13,77,183]. The intervals for repeat testing shown should be determined by clinical judgment and available resources. With CUS, the choice of equipment, technical aspects and operator training must be followed according to expert recommendations [78,82,122]; imaging protocols must be comprehensive and standardised, and age- and sex-specific reference values for CIMT and a detailed assessment of plaques should be employed. CUS is better suited for children and younger patients owing to absence of radiation risk, while CTCA may be useful to assess plaque burden and obstructive stenosis in asymptomatic adult patients. Future developments and refinements in cardiac CT imaging may allow this imaging modality to be fully incorporated into clinical algorithms for assessing atherosclerosis and CHD in FH. All asymptomatic patients should proceed to a functional test, ideally a stress echocardiogram. All ‘positive’ treadmill tests, myocardial perfusion scans and stress echocardiograms should be followed by referral to a cardiologist for the consideration of invasive coronary angiography and appropriate further care [13,78,110]. Patients with more than 70% stenosis of the internal carotid artery should be referred for consideration for revascularization [184,185].

7.6. FH in women

Special considerations apply to the management of FH in women [43,186]. CHD risk is lower in women than men with FH [43,73,187]. Women may therefore be less likely to be treated with a statin at a younger age, but this needs revision according to a detailed family history of premature CVD, the presence of other cardiovascular risk factors and the rate of progression of CIMT [43,55–57,74,75,188]. Low estrogen-containing oral agents, intra-uterine devices and barrier methods are the preferred approaches to contraception in women with FH [186]. The latter two options should be particularly recommended to women older than 35 years who are of childbearing potential. Pre-pregnancy counselling is recommended for all women [66,129,186,187]. Statins and other systemically absorbed lipid regulating medications should be discontinued 3 months prior to planned conception and during pregnancy and lactation [186]. However, women who fall pregnant accidentally while taking a statin could be reassured that the likelihood of any foetal complications is small [189,190]. The risks for future pregnancy and the foetus should be discussed at least annually with all women and girls of childbearing age. Controlling hypercholesterolaemia during pregnancy is particularly important in women with established CHD, and it may also decrease the severity of FH in offspring who inherit the condition [189,191]. Bile acid binding resins are the only safe agents to control hypercholesterolaemia in pregnancy, but only modestly lower plasma LDL-cholesterol levels and poor tolerability related to gastrointestinal side-effects remains a major problem [129,153].

A newer formulation, colesevelam, is more tolerable than the older resins [182]. Pregnant women with heterozygous FH and established CHD, or with homozygous FH, should be considered for LDL-apheresis [95,129]. During breast feeding, resins could be employed to lower LDL-cholesterol where indicated. More data are required on the outcomes of pregnancy in women with FH and on the effect of statins on the foetus in the first trimester; an appropriate registry of patients is recommended.

Particular considerations are also required concerning future pregnancy when one or both members of a couple have FH. In these circumstances, there are a number of options available which enable the couple to avoid having a child affected by FH. These options include not conceiving, adoption (local and overseas), using donor gametes, prenatal diagnosis (PND) using chorionic villus sampling or amniocentesis and pre-implantation genetic diagnosis (PGD) [192,193]. There are a number of issues associated which each of these choices and couples may find it useful to meet with a counsellor who has expertise in reproductive counselling. Couples considering PND or PGD should be referred to a clinical genetics service for counselling and pre-test work up, ideally prior to conceiving.

8. Management of children and adolescents

Fig. 6 summarizes the management of FH in children and adolescents.

8.1. General and lifestyle considerations

All patients, and ideally all immediate family members, should receive expert advice on lifestyle modifications including healthy eating, regular exercise and avoidance of cigarette smoking [12,97,103]. Prevention of obesity, metabolic syndrome and diabetes is paramount in FH [97]. Psychological counselling and social support may be required in special circumstances in certain families with FH [8,84,124]. Parents of affected children must not smoke. Non-cholesterol cardiovascular risk factors such as diabetes, hypertension and obesity should be treated according to relevant expert guidelines [97]. There is clear value in reviewing patients in a paediatric clinic, but we recommend that the paediatrician has some expertise in clinical lipidology and in the prevention of CVD [72]. A good, practical alternative is a family based clinic in which affected children, adolescents and their parents can be reviewed collectively by a multidisciplinary team [123].

Lowest risk FH should be treated with a fat modified diet and plant sterol supplementation [97,103,134,194].
with annual or bi-annual monitoring of weight, growth and developmental milestones. Increased intake of fruit and vegetables may compensate for reduction in plasma carotenoid concentrations in children consuming a plant sterol-ester enriched diet [195]. The value and safety of prescribing statins for children and adolescents with FH is universally recognised [64a,96–98,105,106,108]. As a general guide, boys older than 10 years and girls who have reached menarche should be considered for statin therapy. The specific age at which to introduce a statin is not evidence-based and in practice should be determined by good clinical judgment and assessment of several factors. These include the family history of premature CVD, the prevailing plasma level of LDL-cholesterol, the type of FH mutation identified and the presence of other cardiovascular risk factors (e.g. diabetes mellitus) [1,12,43,55–57,66,73–75,188], as well as the parents’ perceptions and concerns on use of medication [123,196]. The LDL-cholesterol treatment targets in young patients with heterozygous FH will also depend on similar considerations (Fig. 6). The health literacy of parents must be addressed when managing children and adolescents with FH [88,172,173]. Homozygous patients with FH need to be started on pharmacotherapy as soon as practicable after birth and definitely by the age of 10 years [95]. In Australia, to be eligible for PBS subsidy any FH patient aged <18 years must have a plasma LDL-cholesterol >4.0 mmol/L with a positive family history of premature, symptomatic CVD or tendon xanthomata, or known to be positive for an FH causing mutation [116].

### 8.2. LDL-cholesterol targets

The recommended targets for plasma LDL-cholesterol concentration for enhanced and intensive management are $<4$ mmol/L and $<3$ mmol/L, respectively, consistent with other lipid treatment guidelines [14,15,97,98]. An alternative global therapeutic target is a 40% reduction in LDL-cholesterol [12,37,64b]. For highest risk FH with diabetes,
obesity or metabolic syndrome and elevated triglycerides (>2.0 mmol/L), an apoB target of <1.1 g/L may be used [17a,58], noting that there are no published guidelines on the use of apoB or non-HDL cholesterol in children [97,98].

8.3. Pharmacotherapy

The therapeutic targets of LDL-cholesterol in this age group may be attained with a fat modified diet and a statin [97,98], but the addition of ezetimibe [98,197,198] or a bile-acid sequestrant [98,153,199] may be required. In Australia only fluvastatin, pravastatin and simvastatin are registered with the Therapeutic Goods Administration (TGA) for use in adolescents and children older than 10 years [200]; these statins should be initiated at the lowest recommended dose, which should be up-titrated according to cholesterol response and tolerability. Simvastatin and pravastatin have been shown to improve arterial function and carotid atherosclerosis, respectively, in children with FH [104,201]. The efficacy in lowering cholesterol and the short-term safety of more potent statins, such as atorvastatin and rosuvastatin, has been confirmed in children with FH [202,203]. Both of these statins have been approved by the US Food and Drug Administration (FDA) for use in children with FH aged 10 years and above. Ezetimibe is TGA registered for use in adolescents and children older than 10 years [200], with no requirement for dose adjustment. Bile-acid sequestrants can affect the absorption of folate and fat soluble vitamins [153], and appropriate supplementation will be required with longer term use of these agents in children. Colesevelam is the most tolerable form of these agents [182,199], but is not yet registered for use in Australasia or New Zealand. Bile-acid sequestrants should be taken with meals and gastrointestinal side-effects minimised by increasing fluid and fibre intake [153]. Niacin may be indicated for selected patients with homozygous or compound heterozygous FH [98], as well as for heterozygous FH patients with very high Lp(a) and a very early family history of CHD [75]. Niacin should otherwise rarely be used to treat paediatric FH owing to poor tolerability and concerns about increased risk of glucose intolerance, myopathy, hyperuricaemia and hepatitis [98].

By contrast, fibrates are relatively safe and well tolerated in children, but are rarely indicated except in the treatment of FH patients with significant hypertriglyceridaemia (>4 mmol/L) or with a homozygous phenotype [14,97,98]. As with fibrates, higher doses of supplemental omega-3 fatty acid ethyl ester may also be very rarely indicated for patients with severe hypertriglyceridaemia to prevent acute pancreatitis [14,161]. Omega-3 fatty acid ethyl ester may also improve arterial function in children with FH [204]. The recommendations for monitoring drug safety and tolerability in paediatric patients are generally similar to adult FH, but special requirements are noted below and in Fig. 6. More systematically collected long-term safety data are required on the use of statins and other lipid-regulating agents in paediatric FH [205].

8.4. Assessing atherosclerosis

CUS, with specific measurement of CIMT and the detection of early plaques, may be useful in assessing the progression of early carotid atherosclerosis and hence in risk stratification of children [78,122,206]. Longitudinal data in diverse populations support lowering hypercholesterolaemia in children with FH from the age of at least 10 years [206]. CUS could be carried out every two years in moderate risk FH and annually in high risk FH. These intervals are only a guide and should be revised according to clinical context and available resources. Evidence of an increase in CIMT, or development of early atherosclerotic plaques, would be an indication for intensifying treatment in moderate and high risk cases of FH [183] (see Fig. 5). CUS should be carried out by a fully credentialled vascular imaging service and CIMT estimated employing well validated edge-detection software [82,122]; this facility may not be routinely available to many clinics and consequently other paediatric guidelines do not specifically recommend use of CUS in managing FH [64a,b]. Imaging protocols need to be standardised and age- and sex-specific reference data for CIMT employed [82,122]. Contemporary CTCA and calcium scoring should not at present be undertaken in children owing to the radiation doses involved. Uncontrolled dyslipidaemias in young adulthood predicts coronary calcium in middle-aged [207]. We do not consider that serial measurement of the ankle-brachial index plays a role in the management of childhood or adolescent FH, except in very high risk cases including homozygous patients. Measurement of endothelial function, with flow mediated dilatation of the brachial artery, is at present considered a research tool that is not ready for routine clinical practice [122]. Children with a family history of CHD in early adulthood will require non-invasive testing for CHD [13,97] and referral to a paediatric cardiologist is advised [110]. For patients with homozygous, or compound heterozygous FH on LDL-apheresis, regular echocardiography of the aortic valve and aortic root, with estimation of the aortic valve gradient, is recommended [95,97]. These special cases of very high risk FH should be managed jointly with a paediatric cardiologist.

8.5. Clinical monitoring and continuity of care

Recommendations for the follow-up of children and adolescents with FH are broadly similar to adults [14,15,97,98]. However, certain issues require specific attention and review intervals may not need to be as frequent as in adults. Drug tolerability, interactions and safety need careful surveillance [97,98,153,156,163,165]. All children and adolescents on statins require monitoring of physical growth and pubertal development, as well as when indicated plasma levels of hepatic aminotransferases, creatine kinase and creatinine [97,98]. Before commencing statin therapy in adolescent females, specific advice should be given regarding contraceptive choices and the potential risk to the foetus should...
they fall pregnant while on medication [186]. These issues should be considered at each review. Adolescence is an opportune time to evaluate each patient’s understanding of FH and provide age-appropriate education as required. Important issues that should be addressed include: the significance of the autosomal inheritance pattern of FH, with potential offspring having a 50% chance of inheriting the condition; the value of maintaining a healthy lifestyle; the importance of adhering to the medication prescribed and attending appointments for clinical review. Adherence to medical management is a challenge for many individuals with chronic conditions and can be a particular issue in adolescence [170,208]. Family counselling and medication support systems, including nurse or pharmacist co-ordinated programs, to ensure adherence with therapy may be useful, particularly in higher risk patients [166,167,170]. Enrolling the assistance of personnel skilled in managing adolescent problems may be useful [209]. Pharmacists may be utilised for monitoring adherence and flagging non-adherence to medication in the intervals between clinical reviews, as well as for directly improving adherence to medication [166,168]. All children and adolescents with FH should be reviewed at least yearly in a specialist clinic. Highest risk patients should be reviewed at least every 6 months and homozygotes on LDL-apheresis more frequently [95,97,210]. Patients who are well controlled on stable treatment could be managed in primary or shared care. Appropriate clinical pathways should be developed for transitioning and transferring adolescent patients with FH from paediatric to adult clinical care services [211].

9. LDL-apheresis and radical therapy for FH

LDL-apheresis is a radical form of treatment for FH that entails the extracorporeal removal of apoB-containing lipoproteins from the circulation [212,213]. Its use in treating severe FH is supported by published international guidelines [13,95,214–217] and evidence that LDL-apheresis improves CHD outcomes, progression of atherosclerosis and aortic fibrosis, endothelial function and coagulation [212,218,219].

9.1. Indications, patient selection and targets

LDL-apheresis is indicated for patients with homozygous or compound heterozygous FH, as well as for patients with heterozygous FH with documented CHD who are refractory to pharmacotherapy [95,216]. FH patients with very high plasma Lp(a) levels may also benefit from LDL-apheresis [75,217]. Untreated patients with a homozygous phenotype typically have plasma LDL-cholesterol >12 mmol/L and should be treated with maximally tolerated pharmacotherapy for at least 6 months before considering LDL-apheresis [95,220]. Untreated heterozygous patients typically have plasma LDL-cholesterol from 5 to 12 mmol/L [95] and may have true non-responsiveness or intolerance to cholesterol lowering pharmacotherapy. The recommended LDL-cholesterol thresholds for selecting patients for apheresis in Fig. 7 are only an approximate guide and should be modified according to clinical context; an alternative selection criterion could be a <50% reduction in LDL-cholesterol on maximal pharmacotherapy for both homozygous and heterozygous patients.

To be suitable for LDL-apheresis patients must be psychologically and clinically stable and be committed to the treatment. Haemorrhagic diatheses and hypersensitivity to heparin are contra-indications. Clinical assessment should include baseline echocardiogram for aortic stenosis [215]. Patients unsuitable for LDL-apheresis must continue diet and medication. LDL-apheresis is an efficacious, well tolerated and safe treatment for children with severe FH and may be commenced after the age of 5 years in affected individuals [95,97,210]. It should also be considered for pregnant women with uncontrolled FH and stable CHD [221,222].

9.2. Methods for apheresis

There are five apheresis methods that are selective for LDL: membrane differential filtration, immunoadsorption, heparin-induced LDL precipitation, dextran sulphate LDL adsorption and haemoperfusion with direct LDL adsorption [95,212,216,217]. All are comparable at acutely lowering LDL-cholesterol by 50–70% following a single treatment. Plasma exchange (or centrifugal plasma apheresis) may also be used, but its major disadvantage is that it is not selective for LDL. The choice of method will depend on local expertise and resources. Treatment should be carried out in collaboration with a specialty experienced in apheresis, such as a transfusion medicine service, with whom close communication is mandatory. Plasmapheresis and probably cascade filtration should be available via all transfusion medicine services. A dedicated, fully resourced LDL-apheresis unit should also have a variety of methods of apheresis that can be tailored to maximise efficacy and tolerability in individual patients [223]. Vascular access is achieved using bilateral ante-cubital vein cannulation, but a long-term arteriovenous shunt or central venous catheter may be required. Anticoagulation with heparin and citrate is required. Typically, 4–6 L exchanges of plasma are carried out for 2–4 h weekly, biweekly or longer according to therapeutic response.

9.3. Monitoring therapy

The efficacy, safety and tolerability of LDL-apheresis must be monitored at each treatment and the regimen regulated accordingly [215]. The frequency of LDL-apheresis should be adjusted to achieve a time-average plasma LDL-cholesterol concentration between LDL-apheresis therapy of 6.5 mmol/L and 2.5 mmol/L for homozygotes and heterozygotes, respectively (Fig. 7); a mean reduction of >65% in plasma LDL-cholesterol concentration between LDL-apheresis relative to no form of treatment is another possible target. To achieve these targets will usually require
an acute reduction of $\geq 70\%$ in LDL-cholesterol during each procedure. Statins should be continued since they slow the post-exchange rebound in LDL-cholesterol, but use of angiotensin converting enzyme (ACE) inhibitors are contra-indicated with most systems because of a potential bradykinin reaction; [95,217] angiotensin II receptor antagonists are suitable alternatives. The overall incidence of clinical side effects (including hypotension, vasovagal episodes, symptomatic hypocalcaemia and anaemia) during apheresis is less than 5%; if present, these may be corrected using standard medical therapy. Non-specific symptoms such as nausea, fatigue, dyspnoea and abdominal pain respond to temporary discontinuation of therapy. Patients who are persistently intolerant of a particular method of LDL-apheresis should be trialled on an alternative method, including plasma exchange if required [212]. Because of the demands of treatment, psychological status and quality of life should be monitored in all patients. Accordingly, patients and parents of affected children undergoing LDL-apheresis should be offered psychological counselling when indicated.

The long-term efficacy of treatment in homozygous patients should be assessed about every 2 years using CUS for carotid atherosclerosis load, and echocardiography for aortic valve and root involvement, proceeding to stress ECG and possibly coronary angiography, if there is evidence of significant progression of disease [13,78,215,224]. In heterozygous
patients on LDL-apheresis CUS and exercise testing should also be employed at suitable intervals to monitor progression of atherosclerosis [13,183,215]. Many patients undergoing LDL-apheresis will need to be jointly managed with adult or paediatric cardiologists [215,224] and appropriate lines of communication should be established.

9.4. Cost considerations

Besides the complexities of the treatment, the main barrier to using LDL-apheresis is the financial cost. It is estimated that on average each procedure costs AU$2200–2600, so the annual cost of a bi-weekly cycle is approximately AU$53,000 [95]. This is comparable to haemodialysis, but in absolute terms would be less than 1% of the national expenditure on haemodialysis. LDL-apheresis is underutilised in Australia. Health insurance providers, Medicare and tertiary hospitals should support it as a routine service for patients with severe forms of FH.

9.5. Other therapeutic options

As shown in Fig. 7, homozygous patients who are not suitable for LDL-apheresis should be considered for liver transplantation [225,226] or enrollment in clinical trials of novel cholesterol lowering treatments [227], such as apoB-antisense oligonucleotide therapy and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors [228,229]. Alternatively, these new treatments could be made available to patients on a compassionate basis via a special access scheme. Coronary artery bypass surgery and/or aortic valve replacement should be considered prior to liver transplantation according to pre-operative cardiac investigations [215,224]. Patients with heterozygous FH who are not suitable for LDL-apheresis should also be considered for enrollment in clinical trials of new cholesterol lowering treatments [228,229], or an application should be made via a special access scheme for drugs in development for FH. Partial ileal bypass should be considered in heterozygous FH patients who are intolerant of or refractory to pharmacotherapy, noting both the benefits and risks of this surgical procedure [230,231]. There is very limited experience in Australasia with liver transplantation for severe FH. Portocaval shunting carries a high risk of encephalopathy and has now been superseded by LDL-apheresis and liver transplantation; its use in homozygous FH may, however, be considered in countries where newer and more expensive treatments are not available [220]. Finally, there may be a role in the future for gene therapy in treating severe FH [232].

10. Cascade screening: testing and risk notification of families

It is well accepted that the most cost-effective approach to detecting new cases of FH is family cascade screening of close relatives using a genotypic or phenotypic strategy [4,10,31,65,233–236]. Genetic testing of an at-risk individual within a family is often referred to as ‘predictive testing’ [237]; predictive testing on the basis of a known pathogenic genetic variant (i.e. a mutation) is more accurate than predictive testing based on an individual’s clinical phenotype alone, and this also applies to FH [7,8,66]. In a condition like FH, in which the phenotype almost always expresses as hypercholesterolaemia, the descriptor ‘predictive’ could be replaced by ‘presymptomatic’ or ‘diagnostic’ to describe genetic testing [237]. However, because ‘predictive’ describes a more general context and is more widely accepted in clinical genetics it is also used in this document when referring to genetic testing of relatives for FH. Screening for FH using the clinical phenotype alone is a form of ‘diagnostic’ testing, particularly when assessment provides a definite outcome, as in an individual with, for example, a DLCNS > 8 [8,34,44].

10.1. Risk notification

Integral to effective and ethical cascade screening is risk notification [7,8,119,120]. Risk notification is the process of informing relatives that (1) they are at risk of FH, (2) that this may have implications for their health, and (3) that clinical and genetic testing (if applicable) is available to clarify if they do or do not have FH. Fig. 8 provides recommendations, based on expert guidelines and position papers, for undertaking the process of cascade screening whether using a genotypic or phenotypic approach [8,113,119,120,238–240]. Fundamental ethical principles of autonomy, beneficence, non-maleficence and justice are central to this process. Health illiteracy is not uncommon in individuals in the community and must be carefully considered and addressed [87,88,173].

10.1.1. Contacting and informing families

The general protocol for cascade screening should begin by contacting first and then second degree relatives, noting that cases so detected will then become probands for risk notification of their own first and second degree relatives [6–9]. A typical pedigree tree showing the autosomal dominant pattern of inheritance of FH (clinical phenotype expressed) and the yield from cascade screening is shown in Appendix 6. Culturally sensitive strategies may be required when dealing with some ethnic groups [1,241]. Approaching and liaising with community leaders early on is advised to facilitate risk notification and predictive testing occurring in a culturally appropriate way.

The index case should be invited to discuss family risk notification with the clinician or nurse, who will construct a family pedigree and identify first and second degree relatives who should initially be offered testing for FH. Use of a pedigree drawing tool [242] and a fully integrated information management system [243] is strongly recommended to facilitate family assessment, work planning, multidisciplinary care and communication of results to individuals tested and their doctors [9,12,25]. Appendix 7 shows a pedigree tree for
an actual family with FH, illustrating the autosomal dominant inheritance of hypercholesterolaemia, premature CVD and a missense mutation in the LDL-receptor gene. Drawing and detailing such pedigrees is essential for effective implementation of cascade screening, including appropriate risk notification. Clinical genetics services often have well-established protocols for managing families with familial disorders and, where possible, cascade screening should be implemented as a joint collaborative effort of the lipid disorders and clinical genetics services [12,26,115,121,237]. Comprehensive and well validated resources should be employed and developed to accurately convey information to relatives [12,25,37]. The method for risk notification should be tailored to each family, so that relatives may be approached either by the index case, the clinical service, or by both [6,8,119,120,244]. Understanding the reasons why an index case may not consent to cascade screening of other family members is important to provide re-assurance and encourage rapport and disclosure [37,245,246]. Dual risk notification may be the best option: notification by the clinical service alone may lead to relatives feeling aggrieved that they were not informed by their related index case; notification by the index case alone may be taken less seriously than notification by a medical service. Genetic counsellors must be involved when sensitive family issues are identified [8,25,110,121,238].

Index cases who contact relatives should be provided with written information which explains the predictive/diagnostic testing process and implications, and be encouraged to give this to their relatives [12,25,37]. Information and letters sent to relatives should be written in general language to avoid alarm and concern, while emphasizing the voluntary nature of testing [119,120], and the health consequences of a diagnosis of FH being missed when a person decides not to be tested. Communications should also emphasise the health gains of diagnosis and treatment [12,25], as well as the benefits for offspring who may have FH.

In the absence of a response to the first letter, it may be appropriate to make a second approach by letter or telephone call to the family member [37,244]. However, this policy should be discussed with relevant local experts on ethical and risk management matters. Multiple contact attempts could constitute a violation of privacy for some individuals [119,120] and may be counter-productive to the process of cascade screening. Reasons why a relative does not wish to be tested for FH should be explicitly documented [84,86] to facilitate, where indicated, re-approaching them in the future. Electronic methods of communication (e.g. e-mail) could be investigated for their value in enhancing risk notification and cascade screening for FH.

Prior to testing, family members should be given detailed verbal and written information about FH. Written information should again be in clear, non-technical language and preferably accompanied by simplified but explicit diagrams [25,37,119]. Health illiteracy should always be addressed [87,88,173]. Family members who consent to being tested for FH should be offered a standard plasma lipid profile and a genetic test if the mutation is known in the index case. Patients without GPs should be encouraged to visit one as part of the FH counselling process. With consent from the
individual, the outcome of phenotypic or genetic testing for FH should be communicated to their GP and other relevant medical services.

10.2. Co-ordination of cascade screening

Different care pathways may be employed for screening individuals for FH, depending on circumstances and resources [7,25,26,37]. Family members may be tested via the lipid disorders clinic, genetic services or their GP. Depending on knowledge and experience, pre-test counselling may be best undertaken by a specialist medical practitioner, genetic counsellor or specialist nurse. FH specialist nurses should have some competency in genetic counselling [121,247], this being particularly relevant for efficiently co-ordinating an outreach screening service. Phenotypic screening for FH may be carried out by GPs, noting that use of clinical criteria alone may result in the underdiagnosis of FH in a primary care setting [248]. However, GPs should not directly request genetic testing without appropriate specialist training. The future should see more education of GPs in medical genetics and this will increase their role in predictive testing of families for FH [249]. This is particularly important in primary care, given the greater accuracy of genetic testing over clinical criteria in diagnosing FH. FH services that do not employ health practitioners with formal counselling training could consider referral to a clinical genetics service for counselling [26,121,237].

Referral to genetic services should also be considered when contemplating genetic testing in children or adolescents [115,238], and when sensitive family issues are identified. Enquiries concerning PND and PGD for FH are a special indication for referral to a clinical genetics service [192,193]. Genetic counsellors should be involved in training staff caring for FH patients and in supporting GPs and outreach services [7,8,12,26,121].

Cascade screening for FH is best carried out and co-ordinated centrally by a specialist service ideally run collaboratively by lipid disorders and clinical genetics services [12,26,71,115,121,237]. However, relatives may choose to have genetic or phenotypic testing in a primary care setting. In this case, close liaison and communication will be required with their GP. If genetic testing is required, support in pre-test counselling should be given by a clinical geneticist or a genetic counsellor [115,121,237]. If the diagnosis of FH is confirmed genetically, or is highly suspected on phenotypic criteria, GPs should refer the individual to a specialised FH service for advice on treatment and follow-up [12,25,26,38].

10.3. Risk notification without consent

If the index case does not consent to risk notification of family members it is important to explore and understand the rationale behind this [83,245], and in particular the prevailing family dynamics [83,119,120,246]. By maintaining professionalism and continuing to patiently and judiciously explore and resolve key issues [120,246], an effective rapport can often be built with the index case sufficient to revisit the option of risk notification after 6–12 months, or sometimes longer. Referral to a genetic counsellor [121] and involvement of a patient support group for appropriate lay counselling [250–252] may all assist in achieving acceptance of risk notification.

Recent amendments to the Commonwealth’s Privacy Act 1988 in Australia allow private health practitioners “to use or disclose patients’ genetic information, whether or not they give consent, in circumstances where there is reasonable belief that doing so is necessary to lessen or prevent a serious threat to the life, health or safety of their genetic relatives.” (Privacy Legislation Amendment Act 2006 (Cth) amendment to the Privacy Act 1988 (Cth)) [253]. This amendment of the Privacy Act only applies to the private sector [253]. Practitioners employed in the public sector need to refer to the privacy legislation in their own state or jurisdiction concerning the release of information without the consent of the patient [246]. The difference in the privacy laws for public and private patients in Australia is an issue that requires resolution.

A decision to risk notify without the consent of the index case should therefore be very carefully and judiciously taken with attention to privacy legislation in different states, local health service protocols and the NHMRC guidelines [239,246]. Health professionals must understand the genetic basis for FH, take reasonable steps to obtain patient consent and document the process fully before considering risk notification of relatives without consent. The recent NHMRC guidelines [239] are not prescriptive and we urge caution when independently approaching relatives. Nevertheless, FH is a potentially lethal condition and if there are high risk features in the family, such as a strong history of premature CVD, contacting of relatives without consent is justifiable, as indicated in Fig. 8. Refusal of an index patient with FH to share genetic information with relatives is unusual, but when present poses a significant challenge to risk notification and cascade screening [119,120,246]. Best clinical practice implies that disclosure of information without consent during cascade screening for FH should be viewed as a last resort [246]. However, when information is disclosed, it should be the minimum required, avoid identifying the patient or their lack of consent, and should only be made available to family members no further removed than third-degree relatives.

10.4. Insurance cover and genetic testing

All individuals with potential FH should be made aware and understand the implications of genetic testing for certain types of insurance cover [254–256]. Family history of CVD, a clinical diagnosis of FH, plasma level of cholesterol and predictive genetic information could all potentially be employed by the insurance industry to make decisions about exclusion of specific conditions from insurance coverage and setting an insurance policy premium [256–258].
In Australia premiums for insurance products which include cover for life (term), disability/income protection, trauma, business and bank loans (but not private health insurance) are calculated according to the present and past health of the applicant, their family history and any known genetic test result(s) in the applicant, their siblings or their parents [256]. However, insurers who are members of the Financial Services Council have agreed that they will not ask an individual who is applying for insurance coverage to have a genetic test if it has not been done already [259]. Similar conditions apply at present in New Zealand. Better control of hypercholesterolaemia with statins in FH is likely to lower insurance premiums [258].

11. Genetic testing of families

FH is an autosomal dominantly inherited disorder, affected individuals having a 50% chance of passing the causative mutation to each offspring [1–3]. If a pathogenic mutation is identified in an affected index case, predictive testing of relatives using genetic testing is a cost-effective, accurate and acceptable approach for detecting new cases [66,234,260]. However, genetic mutations may not be detected in at least 20% of patients in whom a clinical diagnosis of FH can be confidently made [3,23,45,66,261,262]. Thus, in a smaller but significant proportion of families diagnostic testing should be carried out phenotypically [12,38,68].

One of the main advantages of predictive genetic testing is its ability to definitively confirm or exclude a diagnosis of FH in the relatives of an index case [66]. Fig. 9 outlines the process to be followed when employing predictive genetic testing in cascade screening. The majority of cases of FH are due to mutations in the LDLR, APOB and PCSK9 genes [1–3]. Given that a mutation is known to be present in the index case, genetic testing should be offered to all at-risk family members who present for predictive testing [8,66]. Because of ethical issues involved in genetically testing minors [14,115], it is best and usual practice to first genetically test a phenotypically affected parent. When no consent, or assent, is obtained for genetic testing, the diagnosis of FH can be made phenotypically according to the DLCNS in an adult [8,34,38,44] or to the plasma LDL-cholesterol concentration in a child [46,48,97] (Fig. 9).

Genetic testing of families for FH should be co-ordinated by a specialist ideally run collaboratively by a lipid disorder clinic and clinical genetics [12,26,71,115,121,237]. The psychological consequences of genetic testing must be carefully considered and appropriate education and counselling offered in all individuals [8,66,84,86,115,121,237]. Obtaining informed consent, or parental consent plus child assent in the case of testing children, requires pre-test counselling concerning the implications of the result [115,238]. This is particularly important in children because the future implications are more difficult to anticipate and the consent process via parents or guardians is less direct [115]. Age and developmentally appropriate assent/consent should be obtained from children and adolescents prior to testing and information should be tailored to the child’s level of comprehension [115,121] and the parent’s level of literacy [87,88]. Genetic testing in children can be carried out without invasive venepuncture, for example by using a buccal swab specimen [263].

If the family mutation is not identified by a predictive genetic test, the diagnosis of FH can be excluded in that family member. However, there may be some situations when the family member has significant hypercholesterolaemia (and a phenotype strongly suggestive of FH) but does not carry the pathogenic mutation identified in other family members. Having excluded secondary causes of hypercholesterolaemia [14,15], it may then be appropriate to do a full ‘FH mutation search’ in that individual, including investigation of the extended pedigree. This mutation search should be preceded by appropriate pre-test counselling [115,121,237].

As indicated earlier, when one or both members of a couple has FH and there are concerns about having an affected child, referral for specialist genetic counselling regarding PND and PGD should be considered [192,193]. Couples opting for pre-natal testing should be seen prior to conception. PGD will require detailed assessment by an in vitro fertilization service and a specialised DNA laboratory [264]. Services providing PGD must comply with established laboratory requirements and relevant State and Commonwealth legislation [265].

12. Laboratory approach to genetic testing for FH

12.1. Background

Laboratories providing medical genetic testing in Australia must comply with requirements developed by the National Pathology Accreditation Advisory Council (NPAAC) [264]. Compliance with these standards is regularly assessed in a joint program managed by the Royal College of Pathologists of Australasia (RCPA) and the National Association of Testing Authorities (NATA) [266]. NPAAC requirements address the need for appropriate laboratory resources, governance and supervision, training and continuing accreditation of staff, and appropriate clinical liaison. Medical testing that may be the basis for clinical decision-making must be performed in an accredited laboratory.

Accordingly, genetic testing for FH should be carried out in a NATA/RCPA accredited laboratory [266] that will issue results to the requesting doctor. The process of screening for genetic mutations, confirming identified genetic variants, assessing pathogenicity and issuing a formal report should ideally not take longer than three months. Supported by further evaluation of its cost-effectiveness, we recommend that an application is made for genetic testing for FH to be listed as an MBS item.
In the present context, a gene variant is defined as an alteration in the normal sequence of a gene. Genetic testing of an index case may fail to identify a variant in the genes tested (variant absent) or it may identify a variant (variant present). Identified variants may have been previously reported or be novel. NATA/RCPA accredited laboratories have processes for assessing the likely significance of an identified gene variant and for classifying the variant as clearly pathogenic (a mutation), clearly non-pathogenic (a benign variant) or of uncertain significance (a variant of uncertain significance) [264]. The assessment of significance is discussed in more detail in a later section.

FH has significant locus and allelic heterogeneity, i.e. FH is caused by mutations in a number of different genes and many different pathogenic mutations have been identified in each implicated gene [112,261,267–270]. Thus, the main challenges for genetic testing for FH remain the costs and feasibility of testing the large numbers of patients clinically diagnosed with or suspected to have the condition. As noted earlier, the likelihood of detecting a pathogenic gene variant in an individual suspected of being an index case is directly proportional to the clinical probability of that individual having FH [1,3,66,112,118], as assessed phenotypically by, for example, the DLCNS [34,38,44]. Hence, genetic testing of adults with a phenotypic DLCNS < 3 may not be cost-effective [38,44].

Currently, mutations in three different genes are known to cause FH [1,3,66]. A pathogenic mutation in one of these genes is identified in about 70% of phenotypically definite and 20% of phenotypically probable/possible FH [8,66]. About 95% of the identified mutations are in the LDLR gene and 4–5% in the APOB gene. Mutations are seldom identified in the PCSK9 gene. Detection of a mutation in a family member allows the definite diagnosis of FH to be made, as outlined in Fig. 9. However, failure to detect a mutation does not exclude a diagnosis of FH, particularly if the clinical phenotype is highly suggestive of FH [12,37,66].

There are several reasons why mutations might not be detected in patients with a high clinical suspicion of FH [1,3,66,262]. First, the present laboratory technology is not sufficiently sensitive nor specific for detecting all pathogenic mutations. Second, FH is genetically heterogeneous (caused by mutations in a number of different genes) and not all causative genes have been identified. Clearly, genetic testing is not helpful in families with FH due to mutations in unknown genes as these genes cannot be included in genetic testing. Third, the index case may not have ‘true’ FH, since a family history of hypercholesterolaemia and early CVD is not sufficiently specific for making the diagnosis of FH; some of these patients may have other genetic disorders [66], particularly familial combined hyperlipidaemia [271,272].
Most diagnostic laboratories undertaking FH genetic testing will utilize a number of mutation detection methods [66]. These may include: (1) nucleotide sequence analysis of each of the exons and flanking splice regions (exon by exon sequence analysis, EBESA) of the LDLR, APOB, and PCSK9 genes [3,112,261,270,273]; (2) methods that detect large duplications and deletions in the LDLR gene based on Multiplex Ligation Probe Amplification (MLPA) [274,275]; (3) methods that screen for specific mutations in the LDLR, APOB and PCSK9 genes [260,276–280].

12.2. A protocol for genetic testing

Complete screening for all known FH-causing genes is expensive and time consuming [66]. A laboratory protocol that is likely to be cost-effective for genetic testing (searching for a mutation) an ‘index case’ considered to have phenotypic FH is proposed in Fig. 10. This protocol could form the basis of a standardised, national protocol for genetic testing for FH. We emphasize that laboratories may choose to vary the approach to genetic testing for FH shown in Fig. 10 according to the available resources: for example, laboratories may opt to proceed directly to DNA sequencing for an LDL-receptor mutation of all test samples received [3,66,112,261,270,273]. We recognize that technological advances in genetic testing and the discovery of new genes causing FH will necessitate appropriate modification to the protocol [66,110] in Fig. 10.

The steps proposed in Fig. 10 are as follows; (1) individuals with a DLCNS < 3 (unlikely FH) are not offered genetic testing, because the likelihood of identifying a pathogenic gene variant is low and with currently available technology not cost-effective; (2) genetic testing for FH is offered to all individuals with a DLCNS ≥ 3, which includes all possible, probable and definite phenotypic cases of FH; (3) for individuals with a score of 3–5 (possible FH), to maximize cost-effectiveness, testing could be limited to sequential testing using: Screen 1, employing commercial methods that target specific mutations; [260,280–282] Screen 2, employing MLPA [274,275,283] (Fig. 10); (4) individuals with a DLCNS ≥ 6 could be offered more comprehensive sequential testing: Screen 1, employing commercial methods that target specific mutations; [250,270–272] Screen 2, employing MLPA; [274,275,283] Screen 3, employing sequential EBESA of at least the LDLR gene (the recommended order for EBESA is LDLR > APOB > PCSK9) [3,66] (Fig. 10). All results from commercial chip or kit technology that identify a gene variant as being present should be confirmed using the second validated testing method. This is a requirement of good laboratory practice [264,266] and relates to the potential analytical errors with the commercial methods.

It should be noted that the protocol in Fig. 10 refers to diagnostic testing (mutation searching) for FH in a phenotypically defined ‘index case’. In a predictive testing setting the laboratory will already know the mutation in the index case and there is no need to screen for mutations other than directly testing for the one identified in the family [8,66]. To increase acceptability, genetic testing for FH in children should be available using DNA extracted from either blood or buccal samples [263].

12.3. Assessing the significance of gene variants detected in index cases

Various pieces of evidence are used to determine the significance of an identified gene variant [264] and this clearly also applies to genetic testing for FH [66]. These include the published literature (including database entries), epidemiologic studies, in vitro and (preferably) in vivo demonstration that the variant causes a functional abnormality, and in silico (molecular software) assessment [284,285]. For practical reasons, in silico assessment coupled with search of the literature and established databases [267,286] are the usual primary sources used for assessing the significance of a gene variant. Unfortunately, published literature may in general contain errors, so careful assessment is required. In silico data are also variable in quality, particularly when it comes to assessing splicing mutations [287]. Patients and their managing clinicians should also be aware that a laboratory interprets each genetic test result in accordance with the best information available at the time of the test, and that it is possible that new information may emerge which results in a change in how a genetic test is interpreted.

Particular care needs to be taken when classifying a gene variant as a pathogenic mutation, since it may be used in predictive genetic testing of asymptomatic individuals. If a variant of uncertain significance (either previously reported or novel) is detected, it is not appropriate to regard it as pathogenic. Clinical management of the individual and their family should be based on the plasma lipid phenotype (and other clinical criteria) and not on the genetic test result [12,13,26,38].

Fig. 11 provides a general approach for assessing and reporting the outcome of genetic testing for FH in a phenotypically defined index case. The significance of a gene variant should be assessed as recommended above. The formal laboratory report of the FH variant/mutation should detail the standardised methods used and the evidence supporting the classification [264]. If a pathogenic variant (mutation) is identified the report should also make the recommendation that further relatives be genetically screened for FH [264]. Where no gene variant or pathogenic mutation is detected, the report should include the caveat that such a result does not definitively exclude the diagnosis of FH.

13. The web of care for FH: the optimal service model

Fig. 12 encapsulates the multiple components that should ideally comprise a comprehensive healthcare model for FH. The recommendations and MoC described in this document provide detailed pathways for the principal clinical compo-
Fig. 10. A laboratory protocol for genetic testing an 'Index Case' considered to have phenotypic FH.  

Dutch Lipid Clinic Score ≥ 3 in Index Case
Prioritise >8 definite, 6 – 8 probable, 3 – 5 possible

Consents to Genetic testing

Definite and Probable FH
- Screen 1: Commercial method for detecting specific pathogenic variants
  - Variant absent
  - Screen 2: MLPA
    - Variant absent
    - Screen 3: Comprehensive exon by exon sequencing
      - Variant absent
      - Issue report
        - Include caveat that FH due to rare gene variants/mutations cannot be excluded

Possible FH
- Screen 1: Commercial method for detecting specific pathogenic variants
  - Variant absent
  - Screen 2: MLPA
    - Variant present
      - Confirm by sequencing and / or appropriate alternative method if available
      - Issue report

Variant present
- Assess significance of gene variant (See Figure 11)
"Index case" consents to genetic test

Genetic testing as per Figure 10

Variant detected

- Assess significance of variant *
  - Variant of uncertain significance
  - Benign variant

Pathogenic variant (mutation)

Issue Report
- With appropriate recommendation for testing relatives (See Figure 8 & 9)

No variant detected

Issue Report with caveat that FH cannot be excluded

Fig. 11. Assessment and reporting of the outcome of genetic testing in an ‘Index Case’. *See text for further details.

ents shown in Fig. 12. This MoC represents an overarching system that significantly extends and updates other published service models [12,13,25–28].

13.1. Focus, aims and objectives

Health service provision should focus on three main areas: patient care services, laboratory services, and research and clinical audit. The aims, objectives, expectations, outcomes and key performance indicators for each of these should be clearly identified and documented. Research and audit agendas for FH have been published elsewhere [12,37,288]. Care pathways for the seamless flow of patients between relevant specialties and other health providers, including primary care, should be specified and developed. The general aim of clinical care should be to identify, assess, manage and treat children and adults with FH to the highest level of clinical excellence. The primary therapeutic objective is not only to reduce cardiovascular risk related to elevation in plasma LDL-cholesterol [1,2,12,13], but also to treat other cardiovascular risk factors including obesity, hypertension, type 2 diabetes, metabolic syndrome and smoking [17a,32,33,43,55–57,74,125,127]; psychological and psychosocial factors must also be addressed [8,83–86,124,136,289]. A major long-term objective of health service provision for FH should be to identify most people with the condition in the community, aiming to achieve realistic targets in given time-frame, e.g. 30% detection rate after 3 years of service implementation.

13.2. Co-ordination and integration of care

To achieve the clinical aims and objectives of the health-care model for FH requires a dedicated multidisciplinary service [110] that is best co-ordinated by a lipid disorders clinic [26,71]. This service should be managed by suitably credentialled personnel operating out of departments of internal medicine, endocrinology or cardiology. Physicians who regularly manage patients with FH should have specialist training in clinical lipidology and competencies in the prevention of CVD [26,72], and be credentialled to supervise the training of junior physicians. Uncomplicated patients could be referred back to their GPs for long-term care but should be reviewed annually in a lipid disorders clinic. Existing clinics may need to up-skill their approaches to cascade screening for FH [9,290]. GPs should actively seek index cases in their practice by recognizing the importance of the family history of CVD and marked hypercholesterolaemia [68]. However, the optimal method for systematic identification of FH in primary care needs to be defined and a specific MoC devised.
and tested. Decentralization of the management of FH should be a major objective of future developments. As FH services develop further in the community, the specific roles of general practice and other members of the primary care team will become clearer and inform future MoCs. Outreach lipid clinics in the community would be a useful first step, but clinical protocols need developing and testing. Telehealth may have a role in the management of FH in Australia, but its cost-effectiveness remains to be evaluated. Patients aged <16 years should be seen in a paediatric clinic run by a specialist in metabolic medicine; dietetic counselling is essential in this age group. An integrated adult–paediatric clinic may be useful for certain families. Nurses should be trained in managing patients and families with FH, and preferably have some experience in the prevention of CVD and competency in genetic counselling. Cascade screening, including risk notification, should be co-ordinated by a health practitioner or specialised nurse working out of a central FH clinic or a clinical genetics service, and should include (where required) provision of an outreach service. With appropriate specialist training, nurses could effectively administer genetic counselling. Beyond cascade screening, FH nurses may be involved in several other areas. These include the clinical care of patients, medication support, education and training, audit and research, enhancing multidisciplinary links and working with a patient support group; nurse co-ordinated clinics and multidisciplinary case discussions should be integral to the service. By example, the effectiveness of nurse-led interventions has been demonstrated for management of non-cholesterol CVD risk factors, such as hypertension and diabetes. The role of the dietician is essential, for dietary management and weight regulation is a cornerstone of treatment. Additional input from health and adolescent psychologists and exercise physiologists may be required in special circumstances. Health literacy needs to be appropriately addressed. Suitably trained nurses may have the best overall skills for co-ordinating the workflow necessary for the optimal care of patients with FH. Clinical pharmacists can have a special role in managing non-adherence to medication and in liaising with GPs. The use of lay counselling, particularly in patients who lack understanding of their condition and are non-adherent to treatment, is another promising resource that requires evaluating in the context of FH.

Inter-specialty links

Beyond the lipid disorders clinic strong links are essential with departments of clinical genetics in respect of the need for family and genetic counselling, particularly during the cascade screening process. A genetics centred service may be appropriate for cascade screening, but it may be more effective if genetic counsellors are based in and work out of the lipid disorders clinic. Not all

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Fig. 12. The web of care for FH: the optimal service model.
families or patients with FH require genetic counselling, but some exposure and basic training in the principles of genetic counselling is important for both physicians and nurses who manage FH [72,121]. The general skills of a genetic counsellor may, on the other hand, be also more broadly utilised in an FH service when dealing with certain clinical issues [121], such as adherence with medication [170,208].

Many patients with FH may be diagnosed amongst those attending departments of cardiology, cardiothoracic surgery, stroke medicine and vascular surgery [22,38,60], and close liaison with all these is essential. At least one in twenty people with premature CVD cared for by these specialties may have FH [22,38]. A structured system for the routine screening and accurate detection of FH in these clinical settings is strongly recommended.

An FH service should also have close links with laboratory medicine and access to routine and specialised laboratory and clinical tests [71]. These include routine lipids and lipoproteins, apoB, Lp(a), homocysteine and high sensitivity C-reactive protein (CRP). Genetic testing should be carried out in a NATA/RCPA accredited laboratory [266] that can screen for all the major genes that cause FH. These laboratories must comply with the standards set by the NPAAC [264]. The clinical assessment of patients with FH also involves access to cardiac and imaging facilities, including treadmill testing, myocardial perfusion scanning, CUS and echocardiography [13,65–78]. Close links with the department of cardiology are essential for the referral of symptomatic, or high risk cases, that will require coronary angiography and invasive interventions.

Links with a transfusion medicine unit is important for administering and monitoring LDL-apheresis [215–217]. LDL-apheresis should be offered to all patients with homozygous (or compound heterozygous) FH and to heterozygotes who are not at target LDL-cholesterol and have progressive CHD or are intolerant of cholesterol lowering medications [215–217].

13.3. Administrative and information technology support

The clinical service should be underpinned by appropriate administrative and secretarial support [25,26]. A specialised database for storing clinical and family data and information technology support systems are essential for effective provision of services [25]. Computerised programs should have several key capabilities for dealing with pedigree drawing, work flow management, production of template letters, archiving data, clinical audits and research. Other important requirements include a high level of data confidentiality and security, and compatibility with other healthcare software systems. Favourable experience with one such software program [243] has been reported [294], but requires further evaluation in full clinical service mode. A secure, high quality software system is required to establish and develop a national registry of FH patients that links family members across states. The International Cholesterol Foundation (InterChol) is an integrator and facilitator of communications between clinical services worldwide; its webpage (www.interchol.org/links) provides links to several international bodies that deal with FH. Details of websites that could be useful for clinical services caring for FH are given in Appendix 8.

13.4. Clinical governance: audit, education, training

Efficient clinical governance is fundamental to all aspects of an FH service [37,295]. Clinical governance should entail holding regular multidisciplinary conferences, focusing on the quality and efficiency of all aspects of the service. Retrospective and ongoing clinical audits are essential for monitoring the efficiency of service delivery. A well-designed and comprehensive clinical registry can provide invaluable information for improving the quality of care for FH [296], consistent with requirements for all inherited cardiovascular conditions [110,297]. Continuing education and training of all healthcare providers is essential for professional development and service improvement. Regular journal clubs can inform on recent advances in the diagnosis and care of patients with FH. Essential for clinical governance is a clearly identifiable management structure headed by a medical director and a clinic or nurse manager [71]. Standard operating procedures, staff responsibilities and credentialling, documentation and essential resources must all be clearly defined. Marketing the clinic, increasing the number of referrals, devising an effective business plan and generating income for the service, as well as promoting collaborative research, are all highly desirable requirements for developing an effective clinic service for FH.

13.5. Patient and family support groups

Every effort should be made to initiate and sustain an active association for patients and families affected by FH via a support group [250,251]. This forum provides a network for individuals and families to form an advocacy group to develop and promote services within the community, as well as a nucleus for learning and sharing information that is critical for the detection, management and reduction of risk in families with FH. The perceptions and views of patients and their families are clearly important in developing and improving health services for FH [110]. Patient support for families and the raising of community and government awareness about FH is an important function of the support groups. A national patient support organisation could afford the best means of establishing a national registry of both patients and services, including clinics undertaking cascade screening. Such an FH registry could be incorporated into the Australian National Genetic Heart Disease Registry [297].
13.6. Into the future: chronic care model, commissioning, evaluation

Future design and development of health provision for FH needs to take place within the framework of the Chronic Care Model [298], and hence in a positive policy environment [299]. This will require interacting and establishing partnerships with a wide spectrum of stakeholders, including patient support groups, heart foundations and related non-government organizations, health networks, health economists, policy makers and health ministers. In time, the care of FH could be integrated into national and state services for inherited cardiovascular conditions [110]. There is a major need to increase public and health provider awareness of FH through continuing education programs [288]. Academic health service systems may be ideally suited for co-ordinating and integrating the health care of FH and other inherited cardiovascular disorders, but these need to be developed in Australia [300]. Publishing guidance on the care of FH is one thing, but effectively implementing recommendations is another, a gap well emphasised by a recent report from the UK [301]. Addressing the national and international gaps in the management of hypercholesterolaemia at a community level will benefit the detection and care of patients with FH [174–178]. Programs that are successful in delivering high quality services for FH also have an obligation in advising on and supporting the development of such services at a national and international level. We emphasize that an optimal FH service provides a classical paradigm and standard for the detection and treatment of other disorders that cause premature atherosclerosis that need attention in their own right. Finally, we strongly recommend that our MoC for FH be commissioned and incorporated into healthcare delivery and prevention strategies in our community with a very high level of priority. It should also be subjected to regular auditing and health economic evaluation, thereby allowing the MoC to grow into a standard of excellence for the care of all patients with FH.

Appendix 1. FH Australasia Network Consensus Group and Process

Chair

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Writing committee

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Hospital, Sydney), Emeritus Prof. Trevor Redgrave (Lipid Disorders Clinic, Royal Perth Hospital, Department of Physiology, School of Medicine and Pharmacology, University of Western Australia), Ms Nicola Reid (Cardiovascular Prevention and Lipid Disorders Clinic, Christchurch Hospital, New Zealand), Ms Lynda Southwell (FH Western Australia, Royal Perth Hospital, University of Western Australia), Dr Graeme Suthers (SA Clinical Genetics Service, Genetics & Molecular Pathology Directorate, Women’s & Children’s Hospital, Adelaide), Prof. Andrew Tonkin (Cardiovascular Research Unit, Monash University, Melbourne, Victoria), Prof. Simon Towler (Chief Medical Officer, Health Networks, Department of Health, Government of Western Australia), Prof. Ronald Trent (Department of Molecular & Clinical Genetics, Royal Prince Alfred Hospital, University of Sydney).

Consensus process

The Steering Committee met three times in Adelaide, Sydney and Brisbane, organised and chaired by GFW. A variable number of other contributors attended these meetings or were invited to comment on evolving drafts of the paper via email or telephone. The first meeting discussed a preliminary model of care for FH from Western Australia funded by the Australia Better Health Initiative and based on material initially developed by FH Australasia (GFW, DS). The second meeting reviewed the core evidence on FH (published in the English language on PubMed and webaddresses) and discussed and critically commented on a first draft of the consensus paper written by GFW. GFW, DS, NP and FvB then re-drafted sections of the paper, after reviewing further comments by all members of the group. At the third meeting, the Steering Committee re-examined a pre-final draft of the paper and reached consensus on the principal recommendations of the model of care. GFW then prepared a final draft of the paper. All members approved the final document before submission.

Funding

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Disclosures

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Appendix 2. Dutch Lipid Clinic Network Criteria for FH

Dutch Lipid Clinic Network Criteria for making a diagnosis of FH in adults [34].

<table>
<thead>
<tr>
<th>Criteria Score</th>
<th>Family history</th>
<th>Score</th>
<th>Clinical history</th>
<th>Score</th>
<th>Physical examination</th>
<th>Score</th>
<th>DNA analysis functional mutation in the LDLR, APOB or PCSK9 gene</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First degree relative with known premature coronary and/or vascular disease (Men &lt;55 years, Females &lt;60 years), OR First degree relative with known LDL-cholesterol &gt;95th percentile for age and sex</td>
<td>1</td>
<td>Patient with premature coronary artery disease (age as above)</td>
<td>2</td>
<td>Tendon xanthomata at age &lt;45 years</td>
<td>6</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>First degree relative with tendon xanthomata and/or arcus cornealis, OR Children aged &lt;18 years with LDL-cholesterol &gt;95th percentile for age and sex</td>
<td>2</td>
<td>Patient with premature cerebral or peripheral vascular disease (age as above)</td>
<td>1</td>
<td>Arcus cornealis at age &lt;45 years</td>
<td>4</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/L)</td>
<td>LDL-C ≥8.5</td>
<td>8</td>
<td>LDL-C 6.5–8.4</td>
<td>5</td>
<td>LDL-C 5.0–6.4</td>
<td>3</td>
<td>LDL-C 4.0–4.9</td>
<td>1</td>
</tr>
<tr>
<td>DNA analysis—functional mutation in the LDLR, APOB or PCSK9 gene</td>
<td>Total score</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stratification</td>
<td>Definite FH</td>
<td>Score</td>
<td>Probable FH</td>
<td>Score</td>
<td>Possible FH</td>
<td>Score</td>
<td>Unlikely FH</td>
<td>Score</td>
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<tr>
<td></td>
<td>&gt;8</td>
<td></td>
<td>6–8</td>
<td></td>
<td>3–5</td>
<td></td>
<td>&lt;3</td>
<td></td>
</tr>
</tbody>
</table>


Appendix 3. Simon Broome Criteria for FH

Simon Broome Criteria for the diagnosis of FH [12,41].

**Definite FH**

Raised cholesterol:
- In children (<16 years): total cholesterol > 6.7 mmol/L OR LDL-C > 4.0 mmol/L
- In adults (>16 years): Total cholesterol > 7.5 mmol/L OR LDL-C > 4.9 mmol/L

**AND**

- Tendon xanthomata in the patient or in a first or second degree relative
- OR
  - DNA based evidence of a LDL-receptor, familial defective apo B-100 or PCSK9 mutation

**Possible FH**

Raised cholesterol:
- In children (<16 years): total cholesterol > 6.7 mmol/L OR LDL-C > 4.0 mmol/L
- In adults (>16 years): total cholesterol > 7.5 mmol/L OR LDL-C > 4.9 mmol/L

**AND one of the following:**

- Family history of premature myocardial infarction
- MI at <50 years in second degree,
- MI at <60 years in first degree relatives.
- OR
- Family history of raised cholesterol
- In adult (>16 years), first or second degree relatives: total cholesterol >7.5 mmol/L
- In child (<16 years), first degree relatives: total cholesterol >6.7 mmol/L

Appendix 4. MEDPED Criteria for FH

MEDPED Criteria for the diagnosis of FH [42].

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>1st degree relative with FH TC (LDL-C)</th>
<th>2nd degree relative with FH TC (LDL-C)</th>
<th>3rd degree relative with FH TC (LDL-C)</th>
<th>General population TC (LDL-C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>5.7 (4.0)</td>
<td>5.9 (4.3)</td>
<td>6.2 (4.4)</td>
<td>7.0 (5.2)</td>
</tr>
<tr>
<td>20–29</td>
<td>6.2 (4.4)</td>
<td>6.5 (4.6)</td>
<td>6.7 (4.8)</td>
<td>7.5 (5.7)</td>
</tr>
<tr>
<td>30–39</td>
<td>7.0 (4.9)</td>
<td>7.2 (5.2)</td>
<td>7.5 (5.4)</td>
<td>8.8 (6.2)</td>
</tr>
<tr>
<td>≥40</td>
<td>7.5 (5.3)</td>
<td>7.8 (5.6)</td>
<td>8.0 (5.8)</td>
<td>9.3 (6.7)</td>
</tr>
</tbody>
</table>

TC = total cholesterol.
Appendix 5. Typical examination features of FH

a) Arcus Cornealis

b) Extensor Tendon Xanthomata

d) Achilles tendon xanthomata

Illustrations showing typical examination features of FH
Appendix 6. Hypothetical Pedigree

Hypothetical pedigree tree depicting dominantly inherited phenotype in FH.

Appendix 7. ‘Real case’ Pedigree

Pedigree of actual family with a mutation in the LDL-receptor gene. This pedigree illustrates the dominant inheritance of hypercholesterolaemia and premature CHD in a family with FH (LDL-R gene = c.681C > G (Asp227glu) in exon 4). TC = total plasma cholesterol (mmol/L), MI = Myocardial Infarction, CABG = Coronary Artery Bypass Grafting.
Appendix 8. Selected websites for clinical services

Selected websites that may be useful for clinical services caring for patients with FH.

- **International Cholesterol Foundation**
  www.interchol.org
  New foundation, formed from the merger of MEDPED-International and HEART-EU, that has a strong focus on FH and provides useful links to international websites of interest to patients, researchers and health professionals.

- **HEART UK**
  www.heartuk.org.uk
  Leading UK cholesterol charity that provides extensive resources for health professionals, patients and families on all aspects of the detection and management of FH.

- **Public Health Genomics, UK**
  www.phgfoundation.org
  International foundation that publishes authoritative reports on the role of advances in genomics in health care, and has a particularly excellent document on services for inherited cardiovascular conditions.

- **National Heart Foundation, Australia**
  www.heartfoundation.org.au
  Leading Australian charity that provides a wealth of resources for health professionals and the community on all aspects of primary and secondary prevention of cardiovascular disease.

- **British Heart Foundation**
  www.bhf.org.uk
  Leading British foundation provides excellent resources for health professionals and patients, including informative videos on a wide spectrum of conditions and risk factors.

- **Centre for Genetics Education, New South Wales Health**
  www.genetics.com.au
  Educational arm of NSW Genetic Service that provides genetic information of individuals and families affected by genetic conditions and health professionals who work with them. Activities include workshops and training programs.

- **Human Genetics Society of Australasia**
  www.hgsa.org.au
  Premier Australasian society that provides educational materials, training, polices, guidelines and position statements on all aspects of human genetics.

- **Lipids Online, Baylor College of Medicine**
  www.lipidonline.org
  Established on-line facility, coordinated by Baylor College of Medicine (Houston, Texas, USA), providing resources (slides, visual meetings, commentaries), for clinicians, researchers and educators on several aspects of dyslipidaemia, atherosclerosis and cardiovascular disease.

- **National Lipids Association (NLA), USA**
  www.lipid.org
  US based multidisciplinary specialty society providing education, training, guidelines and position statements on all aspects of the detection and management of dyslipidaemia and related disorders.

- **Learn Your Lipids, NLA**
  www.learnyourlipids.com
  Information for patients with dyslipidaemia, including FH, as provided by the foundation of the National lipid Association in the US.

- **New Zealand Guidelines Group**
  www.nzgg.org.nz
  New Zealand group of experts that specialises in developing and implementing guidelines for best clinical practice; excellent resources on the assessment and management of all cardiovascular risk factors.

- **Rational Assessment of Drugs and Research (RADAR), National Prescribing Service (NPS)**
  www.nps.org.au/health_professionals/publications/nps_radar
  Evidence based assessment of all new drugs, PBS listings and latest research for health professionals provided by the NPS, an independent organisation funded by the Australian Government Department of Health and Ageing.

- **Make Early Diagnosis Prevent Early Death (MEDPED) FH**
  www.medped.org
  US based website of the original MEDPED Project coordinated by the University of Utah School of Medicine (Salt Lake City, UT, USA) focusing on all aspects of the management of FH, including education of patients and families and the first attempt at establishing a US registry.

- **Office of Population Genomics, FH Pilot Cascade Screening Program, Western Australia**
  State funded office that aims to translate genomic knowledge into health benefits for WA health; resources provided relevant to the detection and management of FH.

- **Wales FH Testing Service, Cardiff University**
  www.fhwales.co.uk
  Leading FH service in the UK that provides useful information and resources for clinical practice, including activities of FH Family Forum.

- **FH Support Group of Western Australia**
  www.fhfamilysupportgroup.websyte.com.au
  Website of the first support group in Australia for families with FH; provides relevant information, communication and support services.

- **FH Guideline Implementation Team Toolkit**
  www.heartuk.org.uk/FHToolkit
  Invaluable resource for implementing the seminal NICE guideline 71 on identification and management of FH.

- **FH Australasian Network, Australian Atherosclerosis Society**
  www.athero.org.au/FH
  Website of the FH Australasian Network, updated in 2011

References


