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CONSENSUS STATEMENT

Integrated Guidance for Enhancing the Care of Familial Hypercholesterolaemia in Australia☆

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☆This guidance has been endorsed by the Australian Atherosclerosis Society, Cardiac Society of Australia and New Zealand, National Heart Foundation (Australia), Australian Cardiovascular Alliance, Human Genetics Society of Australasia, European Atherosclerosis Society, International Atherosclerosis Society, FH Foundation, Heart UK, Asian-Pacific Society of Atherosclerosis and Vascular Disease, National Lipid Association (US) and the American Society of Preventive Cardiology.

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Familial hypercholesterolaemia (FH) is a dominant and highly penetrant monogenic disorder present from birth that markedly elevates plasma low-density lipoprotein (LDL)-cholesterol concentration and, if untreated, leads to premature atherosclerosis and coronary artery disease (CAD). There are approximately 100,000 people with FH in Australia. However, an overwhelming majority of those affected remain undetected and inadequately treated, consistent with FH being a leading challenge for public health genomics. To further address the unmet need, we provide an updated guidance, presented as a series of systematically collated recommendations, on the care of patients and families with FH. These recommendations have been informed by an exponential growth in published works and new evidence over the last 5 years and are compatible with a contemporary global call to action on FH. Recommendations are given on the detection, diagnosis, assessment and management of FH in adults and children. Recommendations are also made on genetic testing and risk notification of biological relatives who should undergo cascade testing for FH. Guidance on management is based on the concepts of risk re-stratification, adherence to heart healthy lifestyles, treatment of non-cholesterol risk factors, and safe and appropriate use of LDL-cholesterol lowering therapies, including statins, ezetimibe, proprotein convertase subtilisin/kexin type 9 inhibitors and lipoprotein apheresis. Broad recommendations are also provided for the organisation and development of health care services. Recommendations on best practice need to be underpinned by good clinical judgment and shared decision making with patients and families. Models of care for FH need to be adapted to local and regional health care needs and available resources. A comprehensive and realistic implementation strategy, informed by further research, including assessments of cost-benefit, will be required to ensure that this new guidance benefits all Australian families with or at risk of FH.

Keywords Familial hypercholesterolaemia • Guidance • Adults • Children • Diagnosis • Assessment • Genetic testing • Cascade testing • Management • Organisation of care

Background: Context and Perspective

Low-Density Lipoproteins, Atherosclerosis and Familial Hypercholesterolaemia

Indisputable evidence confirms the causal role of low-density lipoprotein (LDL) particles in the initiation and development of atherosclerotic cardiovascular disease (ASCVD) [1,2]. The classical feature of familial hypercholesterolaemia (FH) is a marked elevation in plasma LDL-cholesterol concentration from birth due to highly penetrant monogenic defects that impair the hepatic clearance of LDL-cholesterol via the LDL receptor [3,4]. FH is the most common co-dominantly inherited cause of premature ASCVD, principally coronary artery disease (CAD). Accordingly, FH is characterised clinically by a personal and family history of hypercholesterolaemia and early CAD [3]. The genetically mediated risk of ASCVD starts to increase from birth and extends over the lifespan. If untreated, the accumulated burden of LDL-cholesterol accelerates the onset of CAD in both men and women of every race and ethnicity [1,3]. The contemporary care of FH provides an exemplar of the value of precision medicine in the prevention of premature ASCVD in families [3–5].

Importance of FH: Tier 1 Genomic Application

Recent epidemiological studies indicate that the overall prevalence of FH in the general population may be as high as 1 in 250 [6–8]. This implies that currently there are approximately 100,000 Australians living with the condition, one in five of whom are children. The prevalence of FH is especially high among people with premature ASCVD [7,8]. The Centers for Disease Control and Prevention have appropriately defined FH as a tier 1 genomic application [5,9], meaning that there is strong evidence that it is a preventable cause of premature disease and death, with significant potential for positive impact on public health and health care savings [7,8,10]. FH is more prevalent than other tier 1 genomic applications, such as hereditary breast and ovarian cancer and

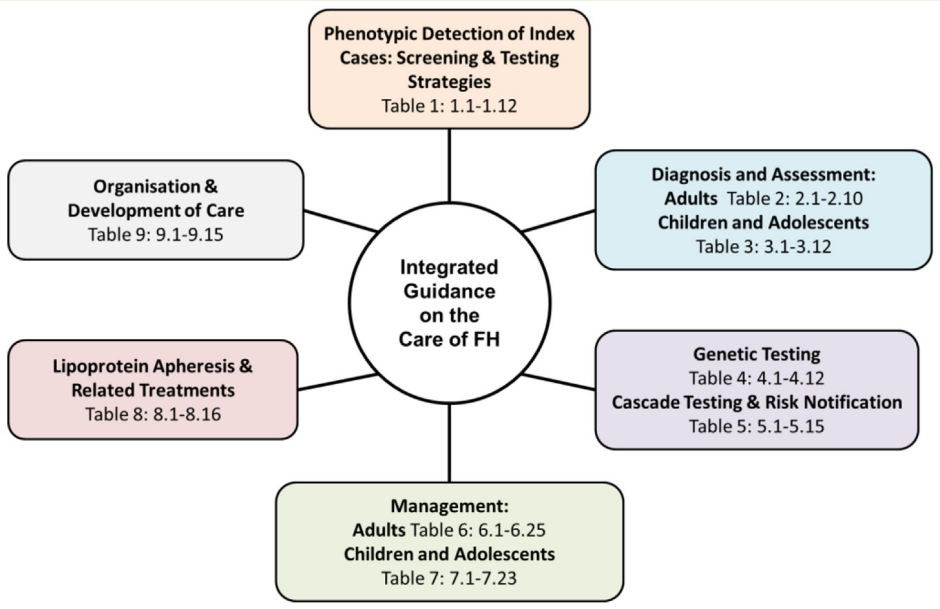

Figure 1 Architecture of the integrated guidance for enhancing the care of patients and families with familial hypercholesterolaemia (FH). The individual recommendations for each of the major components of the guidance are numbered in each box in the Figure and detailed in Tables 1–9.

Lynch syndrome (hereditary non-polyposis colorectal cancer) [5,9]. However, in spite of the importance of FH, less than 10% of individuals (particularly children and adolescents) have been detected, and of those treated, over 80% do not attain guideline recommended LDL-cholesterol targets [3,5]. Targeting the detection of FH as a priority in children and the young could have the greatest impact on the prevention of ASCVD [11–13].

Guidelines, Position Statements and Models of Care on FH

The wide gaps in the care of FH have led to the publication of several international guidelines and position statements [11,14–19]. The FH Australasia Network published one of the first models of care for FH in 2011 [17]. This model was conceived as an adaptive and integrated system, based on theoretical and evidence-based standards, providing the highest quality of health care services to patients and families with FH [17]. Such a framework allows the incorporation of evolving evidence to inform new standards of care, which form the basis for the present guidance. Our original model of care for FH [17] was significant in informing several international guidelines on FH [11,12]. It was updated by an international group of experts [18] and informed a scientific statement from the American Heart Association [11]. The 2014 integrated guidance [18] was assessed using the Appraisal of Guidelines for Research & Evaluation Instrument (AGREE-II) criteria by an independent group of international investigators and ranked as the leading contemporary guidance on FH [20].

Exponential Growth of Knowledge on FH: Review of Evidence

Since publication of the aforementioned guidelines, there has been an exponential growth in published works on several aspects of FH [3]. This includes the following: new knowledge on population prevalence [6–8]; screening methods [3,5,13,21] including use of non-fasting samples [22]; the role of primary care in detection and treatment [23]; new diagnostic gene technologies and genetic testing protocols [24]; methods for risk re-stratification, including estimation of lipoprotein(a) [25–28] and non-invasive cardiovascular imaging [3,29,30]; screening and treatment of children [12,31,32]; the safety and tolerability of statins [33,34]; the efficacy and application of new therapies (eg. proprotein convertase subtilisin/kexin type 9 inhibitors); management of homozygous FH including use of lipoprotein apheresis [35–37]; comprehensive health economic evaluations [38,39]; organisation of services [3], clinical registries [40–42]; role of advocacy and patient support groups [43]; and, definitions of research programs [3,11,44]. This evolving knowledge was reviewed systematically by representatives of the Writing Committee of this guidance in collaboration with international experts in the field in a period up to September 2019. As a consequence, two reviews have been published [3,5] which summarise the essential evidence which has enabled the development of the new recommendations on FH (see Tables 1–9; Appendices A and B; Supplementary Material: Tables 1–9; evidence for statements listed and referenced [References 1–332]). Additional relevant studies published in 2020 were also employed to support guidance statements. Beyond specific guidelines on FH [11,14–19], our recommendations have also been based

Table 1 Phenotypic detection of index cases: screening and testing strategies.

	Class	Level
1.1 Several strategies should be considered for detecting index cases of familial hypercholesterolaemia (FH), including selective, opportunistic and universal screening	2	B
1.2 Index cases should be sought by selective screening of adults with premature atherosclerotic cardiovascular disease (ASCVD), primarily coronary artery disease, and a family history of premature ASCVD and/or hypercholesterolaemia	1	A
1.3 Opportunistic screening, based on a plasma low density lipoprotein (LDL)-cholesterol level of >5.0 mmol/L, should be employed for detecting adults in primary care	1	B
1.4 Universal screening, based on a plasma LDL-cholesterol level >3.5 mmol/L, should be considered before puberty (preferable between 1 to 2 yr of age, coinciding with childhood immunisation) to initially detect children with FH (see 3.5 for diagnostic criteria and see 3.6 and 5.13 for testing of biological relatives)	2	B
1.5 Digital screening (based on key clinical criteria for FH, see Appendix D) of electronic health records should be considered to enable case detection, particularly in primary care	2	B
1.6 Alerts and interpretive comments on laboratory reports on plasma lipid profiles should be employed to enable case detection, including the need to make a phenotypic diagnosis of FH (see Appendix D)	1	B
1.7 The Dutch Lipid Clinic Network (DLCN) criteria (see Appendix D) should only be used to make a phenotypic diagnosis of FH in adults, ideally based on two fasting LDL-cholesterol values estimated by Friedewald's formula or a direct assay; the DLCN criteria should not be used in children and adolescents	1	A
1.8 Non-fasting samples have practical advantages and may be used to approximate LDL-cholesterol by Friedewald's formula when screening for FH; however, they should be used with caution in patients known to have hypertriglyceridaemia	3	B
1.9 In patients with triglycerides >4.5 mmol/L, LDL-cholesterol should be estimated by a direct assay; the diagnosis of FH in such patients should also be based on a 12-hr fasting sample	1	A
1.10 If LDL-cholesterol cannot be measured with a direct assay owing to severe hypertriglyceridaemia, the diagnosis of FH should be reconsidered after therapeutic lowering of triglycerides to below 10 mmol/L	2	C
1.11 The effect of concurrent medication and significant acute illness on LDL-cholesterol should be accounted for: LDL-cholesterol should be adjusted appropriately for use of statin and/or ezetimibe after ensuring adherence to therapy (see Appendix D footnote), particularly if a reliable pre-treatment value is not available; LDL-cholesterol should be repeated after full recovery from acute illness, particularly if the diagnosis of FH is in doubt	1	B
1.12 All patients with suspected FH should be referred to or discussed with a specialist with expertise in lipidology for further assessment (see 2.9, 3.6 and 3.11)	1	C

on new international guidelines for the primary and secondary prevention of ASCVD [49–52], as well as on meta-analyses and systematic reviews on the role of LDL-cholesterol in the inception and development of ASCVD [2,53]. We acknowledge that several novel therapies are in development for managing FH [54–58]. However, with the exception of an angiopoietin-like protein 3 inhibitor for homozygous FH [58], none have been referred to in our recommendations. This is because these agents are still being tested in clinical trials and are not registered in Australia.

National Health Genomics Policy Framework

As reviewed elsewhere, the recommendations of the National Health Genomics Policy Framework [59] have also informed the recommendations for this new model of care for FH. Priority areas include patient-centred approaches, upskilling of the workforce in knowledge of genomics, cost-effective use and evidence-based design of services, and the need for high-quality data collection [59]. Our new recommendations are aligned with the aforementioned priorities. They will accordingly enhance the strategic approach for incorporating genomics into the Australian health care system, as also exemplified by other inherited heart conditions [60]. Genetic testing for FH was listed on the Australian Medicare Benefits Schedule (MBS) in 2020 [61], based on recommendations by the national Medical Services Advisory Committee [62] that were informed by robust cost-effectiveness data collated from an Australian specialist centre [38]. The present guidance includes specific

Table 2 **Diagnosis and assessment of adults.**

	Class	Level
2.1 Secondary causes of hypercholesterolaemia should be excluded before making a diagnosis of familial hypercholesterolaemia (FH) (see Appendix E)	1	A
2.2 The diagnosis of FH should be made using both phenotypic criteria (see 1.7) and genetic testing, but when genetic testing is not available the diagnosis should be made phenotypically (see Appendix D)	1	A
2.3 Detection of subclinical Achilles tendon xanthomata, using standard imaging methods, may be considered to further establish the phenotypic diagnosis of FH and to assess risk of atherosclerotic cardiovascular disease (ASCVD)	3	B
2.4 When possible, genetic testing should be used to confirm the diagnosis of FH, especially if cascade testing (see Tables 4 and 5) is planned	1	A
2.5 Patients with FH should be risk assessed for the presence of major ASCVD risk factors, including elevated lipoprotein(a) [Lp(a)] (see 2.7), which should be employed to guide clinical management	1	B
2.6 Cardiovascular risk prediction equations derived from the general population (eg. the Australian absolute cardiovascular disease risk calculator) should not be used in patients with FH	1	B
2.7 Lp(a) should be measured using an immunoassay that is independent of, and therefore not affected by variation in, the isoform size of apolipoprotein(a); if this is not possible, Lp(a) should be measured using an immunoassay validated as being minimally sensitive to apolipoprotein(a) isoform size; all assays should be calibrated against the World Health Organization/ International Federation of Clinical Chemistry and Laboratory Medicine reference material; results should be reported in nmol/L of Lp(a) particles, with increased risk of ASCVD defined as >100 nmol/L	1	B
2.8 In asymptomatic adult patients with heterozygous FH, cardiovascular imaging, such as coronary artery calcium score (CACS), computed tomography coronary angiography (CTCA) and carotid ultrasonography, may be considered as clinically indicated for identifying subclinical atherosclerosis, but the clinical value is not fully established	3	B
2.9 Adults with homozygous FH should be referred to a specialised centre for assessment and planning of long-term care	1	A
2.10 Adults with homozygous FH should be referred to a cardiologist for clinical assessment and evaluation of ASCVD burden with non-invasive imaging, such as CTCA, carotid ultrasonography, and echocardiography (to assess atheromatous involvement of aortic valve and root), as well as exercise stress testing or functional cardiac imaging, as clinically indicated	1	A

recommendations that will enable the appropriate use of genetic testing for FH in the context of this new MBS item [61].

Methodology for Evidence-Based Recommendations

The quality of the new and diverse evidence in the literature was evaluated systematically by the assigned Writing Committee according to recommended protocols [45–48]. The totality of evidence was in turn systematically employed to inform specific recommendations on the individual components of the model of care of FH, accounting for preferences, values, circumstances and contexts where appropriate [63–65]. The process and basis for the grading of the evidence and recommendations are detailed in Appendices A and B [45–48]. Particular attention was given to include contributions from a wide spectrum of disciplines, consistent with a multi-disciplinary approach, with health consumers accounting for patient values and preferences [65,66]. The totality of published works employed to develop the evidence-informed statements and recommendations are given in the Supplementary Material (Tables 1–9, statements' evidence references 1–332).

It should be emphasised that the evidence for therapeutic interventions in FH was considered principally in respect of the effects on plasma LDL-cholesterol concentration, but where available, was also based on data on subclinical atherosclerosis and atherosclerotic cardiovascular outcomes [17,18]. As in previous publications [17,18], we considered that the absence of randomised controlled trials in FH should not diminish a strong recommendation for an intervention,

Table 3 Diagnosis and assessment of children and adolescents.

	Class	Level
3.1 As in adults, secondary causes of hypercholesterolaemia should be excluded before making a diagnosis of familial hypercholesterolaemia (FH) (see Appendix E)	1	A
3.2 Children with xanthomata, or other stigmata, of homozygous FH, or at risk of homozygous FH, should be tested as early as possible, at least by 2 yr of age	1	B
3.3 Testing of all children with suspected heterozygous FH using phenotypic and/or genotypic strategies should be considered between the ages of 5 and 10 yr	2	B
3.4 The Dutch Lipid Clinical Network (DLCN) criteria should not be employed to make a diagnosis of FH in children and adolescents (see 3.5)	1	A
3.5 A highly probable phenotypic diagnosis of FH should be considered according to the following criteria: (1) an low density lipoprotein (LDL)-cholesterol of >5.0 mmol/L in the absence of a parental history of hypercholesterolaemia or premature atherosclerotic cardiovascular disease (ASCVD), (2) an LDL-cholesterol of 4.0 to 5.0 mmol/L in the presence of a parental history of hypercholesterolaemia or premature ASCVD, or (3) an LDL-cholesterol of >3.5 mmol/L, if a parent carries a pathogenic or likely pathogenic gene variant; LDL-cholesterol should be based on at least two fasting LDL-cholesterol values	2	B
3.6 Children and adolescents with heterozygous FH should ideally be reviewed by a paediatric specialist with expertise in lipidology and access to multi-disciplinary services	1	C
3.7 Genetic testing for FH should generally be offered to diagnose children after a pathogenic or likely pathogenic gene variant has been identified in a parent or first-degree relative (see 4.3 for genetic testing of children as index cases; see Table 5 for cascade testing and counselling)	1	B
3.8 Children with FH should be risk stratified according to age, presence of other ASCVD risk factors, family history of premature ASCVD (especially in first-degree relatives) and the level of LDL-cholesterol and lipoprotein(a) [Lp(a)] at diagnosis, which should collectively guide clinical management	1	B
3.9 In children and adolescents with heterozygous FH, measurement of carotid intima-medial thickness using carotid ultrasonography (carried out in centres with relevant expertise) may be employed to assess ASCVD risk, but its clinical value is not fully established	3	B
3.10 In children and adolescents with heterozygous FH, computed tomography coronary angiography (CTCA) and coronary artery calcium score should not be used to assess ASCVD risk	1	C
3.11 Children and adolescents with homozygous FH should be referred on diagnosis to a paediatric centre with expertise in the care of such patients for comprehensive assessment and planning of long-term care	1	A
3.12 Children and adolescents with homozygous FH should be reviewed by a paediatric cardiologist for clinical assessment and evaluation of ASCVD burden with non-invasive imaging, such as CTCA and carotid ultrasonography, as well as exercise testing or functional cardiac imaging, as clinically indicated	1	A

when there was good evidence for safety and efficacy in lowering LDL-cholesterol (see Appendix B). For certain statements where there was no evidence other than consistency with best clinical practice, the argument from first principles was employed by consensus, as in a previous guidance [18], to define the evidence level (Appendices A and B). Consistent with recent requirements for clinical practice guidelines [65], we attempted to make our guidance statements as practicable and implementable as possible.

Spectrum of Classes of Recommendations and Levels of Evidence

We provide 140 statements in this new guidance on the care of FH; 80 more than in our earlier work on FH [17]. Of the total number of recommendations, 65.0% were classified as strong (class 1), 16.4% as moderate (class 2) and 18.6% as weak (class 3) (see Appendix C). Of overall evidence levels, 25.0% were high (level A), 43.6% were moderate (level B) and 31.4% were low (level C) (see Appendix C). High and moderate recommendations were generally supported by high and moderate levels of evidence (see Appendix C). The levels of evidence for this guidance are compatible with and surpass many other Australian clinical practice guidelines [65]. The evidence-poor components clearly demonstrate that many decisions in the care of FH patients need to be made with minimal or lower quality evidence and that further research may be required [3,11,44]. Compatible with the GRADE system [47], any apparent discordance between level of evidence and class of a recommendation reflected the perceived balance of benefits versus risks or harm by following the recommendation, as assessed by members of the Steering and Writing Committees (Appendices A and B). It also reflected that for certain statements further research was considered unlikely to change the class of recommendation [47]. Beyond the published works

Table 4 Genetic testing.

	Class	Level
4.1 Diagnostic genetic testing and counselling for familial hypercholesterolaemia (FH) should ideally be offered to all adult index cases who have a probable/definite phenotypic diagnosis by the Dutch Lipid Clinic Network (DLCN) criteria (see Appendix D)	1	B
4.2 Diagnostic genetic testing in an adult index case may be considered when there is limited information to establish an accurate phenotypic diagnosis of FH by the DLCN criteria	3	B
4.3 Diagnostic genetic testing of children, as potential index cases, should be considered and offered when parents or first-degree relatives are unknown or deceased, or as part of a universal screening program (see 1.4 and 5.13), or if specifically required to gain access to special therapies for FH (see 7.23)	2	B
4.4 Genetic testing for FH should be carried out in an accredited laboratory using standardised methods to detect pathogenic and likely pathogenic gene variants affecting the low density lipoprotein (LDL)-receptor pathway, and ideally by massively parallel sequencing	1	A
4.5 Variants detected by genetic testing should be classified according to the American College of Medical Genetics and Genomics standards and guidelines or a comparable classification, and should be described in the report using the current Human Genome Variation Society nomenclature	1	A
4.6 If a pathogenic, or likely pathogenic variant, is not detected, FH should not be excluded particularly if the clinical phenotype is strongly suggestive of FH, as the condition may be due to undetected genetic variants	1	A
4.7 Use of polygenic risk scores may be useful in differential diagnosis and risk re-stratification, but their precise value in the management of FH remains to be determined and they should be used with caution	3	B
4.8 Diagnostic genetic testing of index cases with suspected FH should be requested by a specialist with appropriate skills in the care of patients and families with FH (see. 1.12)	1	C
4.9 Where appropriate (eg. rural centres and remote regions), diagnostic genetic testing of index cases with suspected FH may be requested by a general practitioner (GP) guided by a specialist with appropriate skills in the care of patients and families with FH (see 1.12)	3	C
4.10 All health care professionals involved in consenting families for genetic testing and in the clinical management of patients with FH should receive appropriate education in genomic medicine and have basic skills in genetic counselling	1	C
4.11 Simple and pragmatic tools for counselling, consenting and disclosure of genetic information should be developed and tested to support health care professions in providing genetic testing	1	C
4.12 Where both members of a couple have or are at risk of FH, the couple should be referred to genetic services for pre-conception counselling, including the offer of genetic testing if required, discussion of reproductive risks and shared decision making on reproductive planning options (including pre-natal testing and pre-implantation genetic diagnosis)	1	B

supporting the recommendations in this guidance (Supplementary Material Tables 1–9, statements' evidence references 1–332), the clinical care of patients and families with FH must be based on good clinical judgement and shared decision making [66,67].

The Real Challenge: Translation and Implementation of Models of Care

The updating of guidelines and models of care are well aligned with international calls to action on FH [10,68]. These have emphasised the need to enhance awareness, advocacy, screening, testing, diagnosis and treatment of FH, thereby solidifying and extending the 1999 WHO recommendations [69]. The critical challenge that remains is translating the recommendations in this new guidance into health policy and routine high-quality care for all individuals in the population [70–72]. Implementation science affords a unique opportunity for translating recommendations into routine practice to achieve maximal benefit for the population [71,73]. To optimise the care of FH within the contexts of the complex Australian health care system and advances in genomic medicine [59,74], an implementation strategy needs to account for the perspectives and needs of all patients, families, health care providers, stakeholder organisations, health policy makers and the

Table 5 Cascade testing and risk notification of families.

	Class	Level
5.1 Cascade testing (testing of consenting biological relatives of an individual with confirmed familial hypercholesterolaemia [FH]) should be carried out using both a phenotypic and genotypic strategy, but if genetic testing is not available a phenotypic strategy should be used (see 5.3 and Appendix F).	1	A
5.2 Variant specific genetic testing is more cost-effective than phenotypic testing and should be employed to screen family members after a pathogenic, or likely pathogenic, gene variant has been identified in the family	1	A
5.3 When genetic testing is not feasible, the diagnosis of FH in close relatives should be made phenotypically using age- and gender-specific plasma low density lipoprotein (LDL)-cholesterol levels (see Appendix G); the Dutch Lipid Clinic Network (DLCN) criteria should not be employed to make the diagnosis of FH in relatives	1	A
5.4 The process of risk notification of relatives, a crucial part of family care, should be consistent with relevant local legislation and institutional guidelines; risk notification may be indirect (providing a family letter for the notifier to pass to relatives) or direct (clinical service writes to relatives)	1	C
5.5 Where consent for risk notification is refused and that notification carries a risk of breach of confidentiality for the individual refusing, relatives should only be directly notified of their risk if there is specific legislative provision for notification without consent	1	C
5.6 A pro-active approach that respects the principles of privacy, justice and autonomy should be followed	1	C
5.7 Pre- and post-test genetic counselling should be offered to all at risk family members as an integral component of cascade testing	1	A
5.8 Cascade testing and risk notification should ideally be co-ordinated by a well-resourced centre, particularly if employing genetic testing	1	A
5.9 Genetic cascade testing may be undertaken by a general practitioner (GP) with skills in the care of patients and families with FH, under the guidance of an appropriate specialist	3	C
5.10 Genetic cascade testing should initially be prioritised for first-degree relatives of a variant carrier and sequentially extended as additional carriers are identified; if first-degree relatives decline testing, genetic testing should be extended to second-degree followed by third-degree relatives	1	A
5.11 Phenotypic cascade testing should initially be prioritised for first-degree relatives and sequentially extended as additional affected individuals are identified; if first-degree relatives decline testing, phenotypic cascade testing should be extended to second-degree followed by third-degree relatives	1	A
5.12 Cascade testing should ideally be integrated with all strategies for the detection of index cases (see 1.1 to 1.6 and 4.1)	1	B
5.13 Universal screening of children should be coupled with child-parent (reverse) cascade testing (see 1.4 and 3.6)	1	B
5.14 Digital technologies should be developed and tested to enable the process of cascade testing and risk notification of relatives	1	C
5.15 All health care professionals involved in cascade testing and risk notification of families should receive specific training and have basic skills in counselling, as well as in genomic medicine, especially if they are involved in genetic cascade testing	1	C

broader community [70,75]. To have impact, implementation research is essential for improving the outcomes of FH patients over their lifespan [3,10,70]. Implementation has to be mission-driven to fully address the gaps between efficacious and delivered care [71]. This methodology must be embraced and adopted routinely to increase the impact of the new recommendations on improving the care of FH as a national health priority [10,70,75].

Table 6 Management of adults.

	Class	Level
6.1 All adult patients with familial hypercholesterolaemia (FH) should be offered counselling on lifestyle modifications (eg. a fat-modified/heart healthy diet, regular physical exercise, moderation in alcohol intake), interventions to address psychological issues (eg. adjustment disorders, anxiety, depression) and advice to correct all non-cholesterol risk factors (eg. smoking, hypertension, obesity, diabetes) should be provided according to expert recommendations (see 9.3, 9.4 and 9.5)	1	B
6.2 Management should be based on shared decision making and address patient values and preferences; health literacy and barriers to treatment adherence should be addressed and a personalised treatment plan devised	1	B
6.3 In all adult patients with heterozygous or homozygous FH, therapy should initially aim for at least a 50% reduction in plasma low density lipoprotein (LDL)-cholesterol	1	B
6.4 After reaching the target in 6.3, the following therapeutic targets should be considered according to a patient's level of atherosclerotic cardiovascular disease (ASCVD) risk: (1) LDL-cholesterol <2.5 mmol/L (absence of ASCVD or other major ASCVD risk factors); (2) LDL-cholesterol <1.8 mmol/L (imaging evidence of ASCVD alone or other major ASCVD risk factors); or (3) LDL-cholesterol <1.4 mmol/L (presence of clinical ASCVD)	2	B
6.5 In FH patients who develop a recurrent ASCVD event within 2 yr on maximally tolerated statins, a lower primary target for LDL-cholesterol of <1.0 mmol/L may be considered	3	C
6.6 In FH patients with clinical ASCVD, the following secondary targets for therapy may be considered: non-HDL cholesterol <2.2 mmol/L and apolipoprotein B (apoB) <0.65 g/L (stable ASCVD), non-HDL cholesterol <1.8 mmol/L and apoB <0.5 g/L (recurrent ASCVD events)	3	C
6.7 Maximally tolerated high potency statins (eg. atorvastatin or rosuvastatin) with or without ezetimibe, and a fat-modified, heart-healthy diet, with or without plant sterol (or stanol) supplementation, should initially be employed to achieve the above treatment targets	1	A
6.8 A proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor should be employed if treatment targets are not achieved with maximally tolerated statins, ezetimibe and diet	1	A
6.9 Bile acid sequestrants, niacin or fibrates may be considered to further lower LDL-cholesterol	3	B
6.10 If an adult patient with heterozygous FH aged between 18 and 30 yr has been treated from childhood and does not have evidence of ASCVD, the LDL-cholesterol treatment target need not be as intensive as above (see 6.3 and 6.4)	3	C
6.11 Fasting samples should be used to assess LDL-cholesterol responses to the initiation of and change in drug therapy, as well as to monitor LDL-cholesterol in patients with unstable plasma lipid profiles or elevated triglycerides	1	B
6.12 Non-fasting samples should be considered for convenience to monitoring LDL-cholesterol in patients who are on stable drug therapy and do not have elevated triglycerides	2	B
6.13 Patients with statin intolerance should be assessed and investigated according to established guidelines and should be treated with non-statin therapies, including ezetimibe and PCSK9 inhibitors, to achieve LDL-cholesterol treatment targets	1	A
6.14 Low-dose aspirin may be considered in asymptomatic FH patients at higher risk of ASCVD (eg. not at LDL-cholesterol target, marked elevation in Lp(a), diabetes, adverse findings on cardiovascular imaging) who are not predisposed to bleeding	3	C
6.15 In FH patients with clinical ASCVD, or diabetes, on maximally tolerated statins and ezetimibe and with elevated triglyceride levels (1.5–5.6 mmol/L), the addition of high-dose, high-purity omega-3 fatty acids (especially 4 g/d of pure eicosapentaenoic acid ethyl ester) should be considered to further reduce ASCVD risk	2	B

Table 6. (continued).

	Class	Level
6.16 Adult patients with FH should continue cholesterol-lowering drug therapies during acute illness, such as respiratory infections, unless their use is specifically contra-indicated	1	C
6.17 Adult patients with FH, especially those with ASCVD or older than 65 yr, should be offered influenza, pneumococcal and related vaccines as a preventive measure against respiratory infections and acute ASCVD events	1	C
6.18 Plasma levels of hepatic aminotransferases, creatine kinase, glucose and creatinine should be measured before starting and dose titrating drug therapy. All patients on statins should have hepatic aminotransferases monitored; creatine kinase should be measured when musculoskeletal symptoms are reported; glucose and glycated haemoglobin should be monitored, particularly if there are risk factors for diabetes	1	B
6.19 All women of child-bearing age with FH should be offered pre-pregnancy counselling, with individualised and appropriate advice on contraception to minimise cardiovascular risk, before starting a statin and this should be reinforced at annual review	1	B
6.20 Statins and other systemically absorbed cholesterol regulating drugs should be discontinued 3 mo before planned conception, as well as during pregnancy and breastfeeding	1	B
6.21 In women with homozygous FH and clinical ASCVD, use of statins and ezetimibe may be considered after the first trimester, particularly if lipoprotein apheresis is not feasible	3	B
6.22 Although coronary artery calcium score (CACS) may be useful for initial risk stratification in asymptomatic patients with FH prior to commencing a statin (see 2.8), it should not be used to monitor the efficacy of therapy	1	B
6.23 In asymptomatic patients with heterozygous FH, carotid ultrasonography and computed tomography coronary angiography (CTCA) may be used for monitoring the efficacy of cholesterol-lowering therapy, noting that the clinical value of these investigations is not fully established	3	B
6.24 In adults with homozygous FH, carotid ultrasonography, CTCA, echocardiography and exercise stress testing should be employed (every 5 yr or as clinically indicated) to assess progression of coronary ASCVD, carotid ASCVD, atheromatous involvement of aortic valve/root, and inducible myocardial ischaemia, respectively, with the aim of guiding overall management, including the intensity of cholesterol-lowering therapy	1	B
6.25 Lomitapide and evinacumab may be considered, via special access or compassionate use schemes, in all patients with homozygous FH and rapidly progressive ASCVD, as adjunctive treatments to diet and other drugs, to further lower plasma LDL-cholesterol, particularly if lipoprotein apheresis is not feasible	3	B

Table 7 Management of children and adolescents.

	Class	Level
7.1 All patients and families with familial hypercholesterolaemia (FH) should be offered counselling on lifestyle modifications (eg. a fat-modified/heart healthy diet, regular physical exercise), interventions to address psychological issues, and advice to correct or prevent all non-cholesterol risk factors (especially smoking); lifestyle counselling on primordial prevention (i.e. the development of risk factors) is particularly important (see 7.16, 9.3 and 9.4)	1	B
7.2 Management should be based on shared decision making with parents and all children and adolescents, with a developmentally appropriate and inclusive approach, and barriers to treatment adherence addressed	1	B
7.3 In children and adolescents with heterozygous FH, the initiation of statin treatment should be considered at age 8 to 10 yr irrespective of gender; plasma LDL-cholesterol targets in children and adolescents need not be as intensive as in adults	2	B
7.4 Earlier initiation of treatment with statins (see 7.3) should be considered in FH patients with a particularly adverse family history of atherosclerotic cardiovascular disease (ASCVD) (related specifically to FH) or who have other major ASCVD risk factors (see 7.21 for statement on homozygous FH)	2	B
7.5 In children with FH between the ages of 8 to 10 on a suitable diet, a treatment target of low density lipoprotein (LDL)-cholesterol <4.0 mmol/L or a 30–40% reduction in LDL-cholesterol may be considered	3	C
7.6 In children with FH older than 10 yr on a suitable diet, a treatment target of LDL-cholesterol <3.5 mmol/L or a 50% reduction in LDL-cholesterol may be considered	3	C
7.7 Statin therapy with or without ezetimibe, and a fat-modified/heart healthy diet, with or without plant sterol (or stanol) supplementation, should be employed to achieve the above treatment targets	1	A
7.8 Statins licenced in Australia for use in this age group should be employed: these include pravastatin, fluvastatin and simvastatin; ezetimibe is licenced from the age of 10 yr and should be used accordingly	1	A
7.9 The use of atorvastatin and rosuvastatin should be considered in heterozygous FH according to clinical indications and shared decision making	2	A
7.10 The use of a proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitor may be considered in heterozygous FH according to clinical indications and shared decision making, noting that experience with and long-term safety of this drug class is limited in this age group	3	B
7.11 The use of maximal doses of potent statins and ezetimibe should be considered in homozygous FH children as early as possible, ideally by the age of 2 yr	2	B
7.12 Fasting samples should be used to assess LDL-cholesterol responses to the initiation of and change in drug therapy, as well as to monitor LDL-cholesterol in patients with unstable plasma lipid profiles or elevated triglycerides	1	B
7.13 Non-fasting samples are particularly convenient in children and should be considered for monitoring LDL-cholesterol in patients who are on stable drug therapy and do not have elevated triglycerides	2	C
7.14 Although statins and ezetimibe can be safely used in children, weight, growth, physical and sexual development, and well-being should be monitored in this age group	1	A
7.15 Plasma levels of hepatic aminotransferases, creatine kinase, glucose and creatinine should be measured before starting and dose titrating drug therapy. All patients on statins should have hepatic aminotransferases monitored; creatine kinase should be measured and compared to pre-treatment levels when musculoskeletal symptoms are reported; glucose should be monitored, particularly if there are risk factors for diabetes	1	B
7.16 All adolescent girls with FH should be offered pre-pregnancy counselling, with individualised and appropriate advice on contraception to minimise cardiovascular risk, before starting a statin and this should be reinforced at annual review	1	B
7.17 Shared care between paediatric specialists and general practitioners (GPs) should be considered for managing well-controlled and lower complexity patients with FH	2	C

Table 7. (continued).

	Class	Level
7.18 Management should focus on the nuclear or the immediate family, with at least an annual review of children; non-adherence should be addressed	1	C
7.19 Transition of adolescents to young adult services should be considered early and planned in advance, with particular support given to enable ongoing self-management and shared care into adulthood	2	C
7.20 In children and adolescents with heterozygous FH, carotid ultrasonography (carried out in centres with relevant expertise) may be employed to monitor therapy, but its clinical value is not fully established	3	B
7.21 In children and adolescents with homozygous FH, treatment should commence as soon as possible after diagnosis: the LDL-cholesterol target should be similar to adults (see 6.3 and 6.4), which may require addition of a PCSK9 inhibitor to a statin and ezetimibe, as well as the use of lipoprotein apheresis (see Table 8)	1	B
7.22 In children and adolescents with homozygous FH, computed tomography coronary angiography (CTCA), carotid ultrasonography, echocardiography and exercise stress testing should be employed as indicated (with a frequency determined by age, disease severity, radiation exposure, or as clinically indicated) to assess progression of coronary ASCVD, carotid ASCVD, atheromatous involvement of aortic valve/root, and inducible myocardial ischaemia, respectively, with the aim of guiding overall management, including the intensity of cholesterol-lowering therapy	1	B
7.23 Lomitapide and evinacumab may be considered, via special access or compassionate use schemes, in all patients with homozygous FH and rapidly progressive ASCVD, as adjunctive treatments to diet and other drugs, to further lower plasma LDL-cholesterol, particularly if lipoprotein apheresis is not feasible	3	C

Table 8 Lipoprotein apheresis and related treatments.

	Class	Level
8.1 Lipoprotein apheresis should be considered in all patients with homozygous or severe heterozygous FH who cannot achieve low density lipoprotein (LDL)-cholesterol targets (see 6.3, 6.4 and 7.21) despite maximally tolerated drug therapy, including proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors	2	A
8.2 Lipoprotein apheresis should be considered in children with homozygous FH by the age of 5 and no later than 8 yr	2	B
8.3 Lipoprotein apheresis may be considered in adult heterozygous FH patients with progressive clinical atherosclerotic cardiovascular disease (ASCVD) who cannot achieve LDL-cholesterol targets despite maximally tolerated drug therapy, including PCSK9 inhibitors, and who have residual elevation in lipoprotein(a) [Lp(a)] >150 nmol/L	3	C
8.4 Lipoprotein apheresis should be considered in pregnant women with homozygous or severe heterozygous FH, especially those with clinical ASCVD in whom the use of cholesterol-lowering therapy is not feasible	2	B
8.5 Lipoprotein apheresis should be carried out in a centre with relevant experience by trained staff, who should be involved in regular multi-disciplinary team meetings	1	C
8.6 Use of existing clinical infrastructure (e.g. haemodialysis, transfusion, vascular surgery services) should be considered for improving the quality and accessibility of apheresis services	2	C
8.7 If lipoprotein apheresis is not available or feasible (e.g. homozygous FH children with small blood volumes), the use of therapeutic plasmapheresis (which is more widely available) may be considered	3	C
8.8 Diet and drug therapy to lower LDL-cholesterol should be continued during treatment with lipoprotein apheresis	1	A
8.9 Lipoprotein apheresis should be carried out using established techniques and procedures at a frequency of once per wk or every 2 wk, according to feasibility, patient preferences and achieved plasma LDL-cholesterol targets (see 6.3 and 6.4)	1	A
8.10 The efficacy of lipoprotein apheresis should be estimated as the time-averaged mean plasma LDL-cholesterol concentration between sequential procedures using the Kroon formula, as applicable to heterozygous and homozygous FH	1	B
8.11 The frequency of lipoprotein apheresis and intensity of combination drug therapy, including use of a PCSK9 inhibitor (injected subcutaneously immediately after apheresis), should be adjusted according to achieved LDL-cholesterol targets (see 6.4)	1	B
8.12 Reduction in the frequency, or discontinuation, of lipoprotein apheresis may be considered when combination therapy with a PCSK9 inhibitor achieves an LDL-cholesterol well below the recommended targets (see 6.4)	3	C
8.13 The efficacy, tolerability and safety of lipoprotein apheresis, as well as its impact on the quality of life of patients, should be reviewed every few months or as clinically indicated	1	B
8.14 The effect of lipoprotein apheresis on progression of ASCVD should be monitored in FH patients, as clinically indicated, using appropriate imaging modalities, including computed tomography coronary angiography (CTCA), carotid ultrasonography and echocardiography (for aortic valve and root involvement), as well as with exercise stress testing or functional cardiac imaging (see 6.24 and 7.22)	1	B
8.15 Lomitapide and evinacumab may be considered, via special access or compassionate use schemes, as an adjunctive to diet and other drugs, to further lower plasma LDL-cholesterol in homozygous FH on lipoprotein apheresis (see 6.4, 6.8 and 8.11), particularly in patients who have two LDL-receptor null alleles	3	B
8.16 Orthotopic liver transplantation should be considered for younger patients with homozygous FH who have rapid progression of ASCVD or aortic stenosis, who cannot tolerate lipoprotein apheresis (see 8.13), or whose plasma LDL-cholesterol cannot be adequately lowered (see 6.3, 6.4, 7.21 and 8.9) with diet, drug treatment and lipoprotein apheresis	2	C

Abbreviation: PCSK9, proprotein convertase subtilisin/kexin type 9.

Table 9 Organisation and development of care.

	Class	Level
9.1 The design and implementation of models of care for familial hypercholesterolaemia (FH) should be based on the foundational principles of public health, as well as precision and preventative medicine	1	A
9.2 Health care pathways should be developed to meet the needs of local, regional and remote communities, and their acceptability to health consumers and health care professionals (including primary care), as well as their cost-effectiveness and value, should be reviewed regularly	1	C
9.3 Specialist services should be designed to cover a broad continuum of care for all patients with FH, encompassing both public and private sectors, and should employ multi-disciplinary strategies that are closely integrated with primary care	1	C
9.4 Specialist care should have access to lipidology, cardiology, endocrinology, paediatric, genetic, imaging, transfusion medicine, nursing, dietetic, psychology, pharmacy practice, pathology and telehealth services	1	C
9.5 General practice is central to the continuity of care of all FH patients and their families and should accordingly be actively involved in screening, diagnosis, supporting families, shared care with other specialties, managing cholesterol-lowering medication and multi-morbidities, and implementing context-specific models of care for FH	1	C
9.6 Cascade testing and risk notification should ideally be undertaken by trained staff and co-ordinated by a centralised service that is well-resourced (eg. includes clinical and allied health staff, information technology and statistical support, telemedicine and educational facilities)	1	A
9.7 Cascade testing in primary care should be supported by adequate capacity and infrastructure and collaborate closely with a centralised service (see 9.6)	1	C
9.8 Well controlled and lower complexity patients (see 2.5, 2.8 and 3.8) should, in most cases, be managed in primary care	2	C
9.9 Less well-controlled and higher complexity patients (see 2.5, 2.9, 3.6, 3.8, 3.11, 3.12 and Table 8) should be managed by specialists with expertise in the management of FH, with the option of shared management with primary care	1	C
9.10 All health care professionals involved in the care of FH should receive appropriate education and skills training in cardiovascular prevention, professional counselling and genomic medicine (see Appendix H).	1	C
9.11 Services should establish partnerships with academic and professional organisations to enhance teaching, training and research (see Appendix H)	1	C
9.12 The existing registry of patients and families (The FH Australasia Network Registry) should be maintained for clinical, research and audit purposes; it should be developed to include patient-centred capabilities, coverage of all health care services (including lipoprotein apheresis), and linkage to other clinical quality and outcomes registries	1	C
9.13 The national coding systems for FH should be employed in primary and specialist care to improve the precision of data acquisition and linkage, and their utilisation for audit, research and development of health policy	1	C
9.14 The design of adaptive models of care should be underpinned by a research agenda that includes population and basic science, clinical research, patient-centred research, and implementation strategies	1	A
9.15 An advocacy and support group of patients and families should be established for enhancing public, government and health care provider awareness, as well as for improving the total quality of care of FH	1	B

Summary of Guidance Statements

Tables 1 to 9 summarise the Guidance Statements for Enhancing the Care of Familial Hypercholesterolaemia.

- Classes of Recommendation are included (1 = Strong, 2 = Moderate, and 3 = Weak); as are,
- Levels of Evidence (A= High, B = Moderate, and C= Low).

Conversion Factors relevant for some Statements are:

- Low density lipoprotein (LDL)-cholesterol: conversion from mmol/L to mg/dL, multiply mmol/L by 38.67;
- Triglycerides: conversion from mmol/L to mg/dL, multiply by 88.57.

For details of consensus process, assessment of evidence and development of recommendations, see Appendices A and B; for the supportive evidence see the Supplementary Material (Statements in Tables 1 to 9 linked to listed References).

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GFW has received honoraria for advisory boards and research grants from Amgen, Arrowhead, Esperion, Gemphire, Kowa, Novartis, Pfizer, Sanofi and Regeneron.

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CKC has participated either as a participant or speaker in educational meetings sponsored by pharmaceutical companies that make lipid-lowering therapies.

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Endorsements

This guidance has been endorsed by the Australian Atherosclerosis Society, Cardiac Society of Australia and New Zealand, National Heart Foundation (Australia), Australian Cardiovascular Alliance, Human Genetics Society of Australasia, European Atherosclerosis Society, International Atherosclerosis Society, FH Foundation, Heart UK, Asian-Pacific Society of Atherosclerosis and Vascular Disease, National Lipid Association (US) and the American Society of Preventive Cardiology.

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Appendices. Supplementary Data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.hlc.2020.09.943.

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Appendix A. Author provenance, evidence review, consensus process, and endorsements

Selection of Committees and Contributors

The Steering and Writing Committees were selected by board members of the Registry of FH Australasia Network (Australian Atherosclerosis Society, AAS) for having expertise in lipidology, cardiology, pathology, genetics, dietetics, endocrinology, general practice and paediatrics. Contributors were selected from a wide spectrum of medical and allied health specialties, including general practice, general internal medicine, genomic medicine, nursing, pharmacy practice, and health consumers from advocacy groups to account for variability in patient values and preferences; researchers with relevant expertise in genetics, implementation science, health economics and FH also contributed to the document.

Evidence Review

The Steering Committee decided collectively that the structure of and approach to this guidance should be based on a previous guidance on FH that had received a top ranking by an independent group employing the Appraisal of Guidelines for Research & Evaluation Instrument (AGREE-II) assessment criteria [20]. The evidence for the development of this new guidance was based on two peer-assessed reviews of FH [3,5], that were co-authored by members of the steering committee, as well as on additional published works. For the review papers, a literature search of the English language was undertaken between January 2014 and September 2019. The search employed the PubMed database with search string (all fields) "familial hypercholesterolemia" or "familial hypercholesterolaemia". GFW and JP assessed the titles and abstracts of all the articles identified and selected those that were most novel and valuable for informing the components of the model of care for FH. Additional published works were searched for using the above search terms in 2020 to generate relevant publications, which were also provided *ad hoc* by the Writing Committee and by individual contributors up to 31 May 2020.

To update the guidance, the Writing Committee employed these publications, as well as specialist clinical experience and expert opinion. The published works which informed the evidence and recommendations are shown in the Supplementary Material (Tables 1–9; 332 references). The first draft of the guidance statements was produced by GFW and JP. Four (4) core workshops chaired by GFW were held by video conference between December 2019 and January 2020. The fourth workshop focussed exclusively on paediatric aspects of FH. The workshops include all members of the Steering Committee and members of the Writing Committee that covered the essential sub-specialties. The agenda focussed on discussion of the evidence and statement development, and consolidated the statements for each of the recommendations, which were designated both a Class of Recommendation and a Level of Evidence according to the protocol in Appendix B. (see Supplementary Material for references to the evidence supporting the statements). The totality of the evidence was assessed to inform the recommendations.

Document Review and Approval

The majority view (>80%) was employed to reach a consensus on the Class of Recommendation and Level of Evidence on the earlier drafts of the guidance. The statements were reviewed and edited by smaller sub-specialty working groups (specifically in genetic testing, cascade testing, risk notification, cardiovascular imaging, general practice and primary care). These discussions were arranged by the chair via telephone or email communication. All revised statements were subsequently circulated to all contributors for comment. Specific queries and disagreements with statements were resolved via telephone or email discussion with GFW, who then reached full agreement, via email and/or videoconference, with members of the Steering and the Writing Committees, as indicated by specialty. The writing committee examined the pre-final draft of the guidance and reached full consensus on the recommendations and wording of statements. All contributors reviewed and commented on evolving drafts of the document and approved the final version before submission.

Endorsements

Prior to publication, the full FH guidance with Supplementary Material was reviewed for endorsement by assigned members of the Cardiac Society of Australia and New Zealand (CSANZ), National Heart Foundation (Australia), Australian Cardiovascular Alliance, Human Genetics Society of Australasia, European Atherosclerosis Society, International Atherosclerosis Society, FH Foundation, Heart UK, Asian-Pacific Society of Atherosclerosis and Vascular Disease, National Lipid Association (US) and the American Society of Preventive Cardiology.

Appendix B. Classes of Recommendations and Levels of Evidence used to develop the guidance on FH.

Classes of Recommendations[a]	
Strong recommendation: There is high certainty based on the evidence that the net benefit is substantial *Wording: Should be performed; can be trusted to guide practice*	Strong = 1
Moderate recommendation: There is moderate certainty based on the evidence that the net benefit is moderate to substantial, or there is high certainty that the net benefit is moderate *Wording: Should be considered; can be trusted to guide practice in most situations*	Moderate = 2
Weak recommendation: There is at least moderate certainty based on the evidence that there is a small net benefit *Wording: May be considered; can be trusted to guide practice, but care should be taken in its application*	Weak = 3
Levels of Evidence[b]	
Highly certain about the estimate of effect; further research is unlikely to change our confidence in the estimate of effect *Basis: Randomised-controlled trials/meta-analyses/systematic reviews/good quality diagnostic studies*	High = A
Moderately certain about the estimate of effect; further research may have an impact on our confidence in the estimate of effect and may change the estimate *Basis: Good quality clinical or observational studies*	Moderate = B
Low certainty about the estimate of effect; further research is likely to have an impact on our confidence in the estimate of effect and is likely to change the estimate *Basis: Expert opinion based on clinical experience or argument from first principles*[c]	Low = C

The above systems for grading recommendations and evidence was agreed by consensus at workshops on the development of lipid position statements, held by the Australian Atherosclerosis Society (AAS) in 2018, attended by members of the Steering Committee, members of the AAS Clinical Council and various contributors.

The published works employed as evidence to support individual recommendations are specified in the Supplementary Material (Tables 1 to 9, and References 1 to 332).

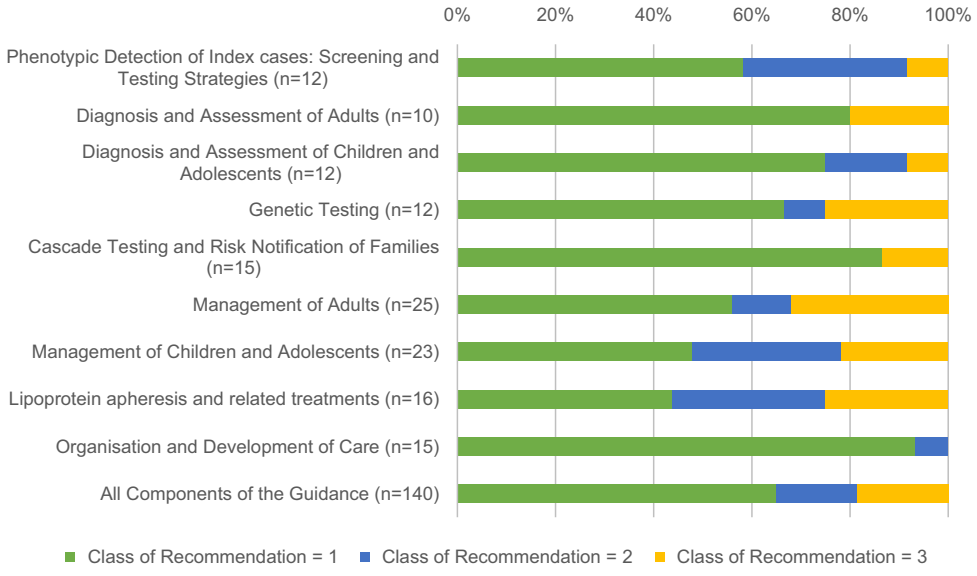
[a]This system was based on the American Heart Association/American College of Cardiology [45] and the National Lipid Association [46] cholesterol guidelines.

[b]This system was based on the American Heart Association/American College of Cardiology [45] and the National Lipid Association [46] cholesterol guidelines, and adapted from the original GRADE system of evidence rating [47], which is in turn endorsed by the National Health and Medical Research Council Guidelines for Guidelines [48].

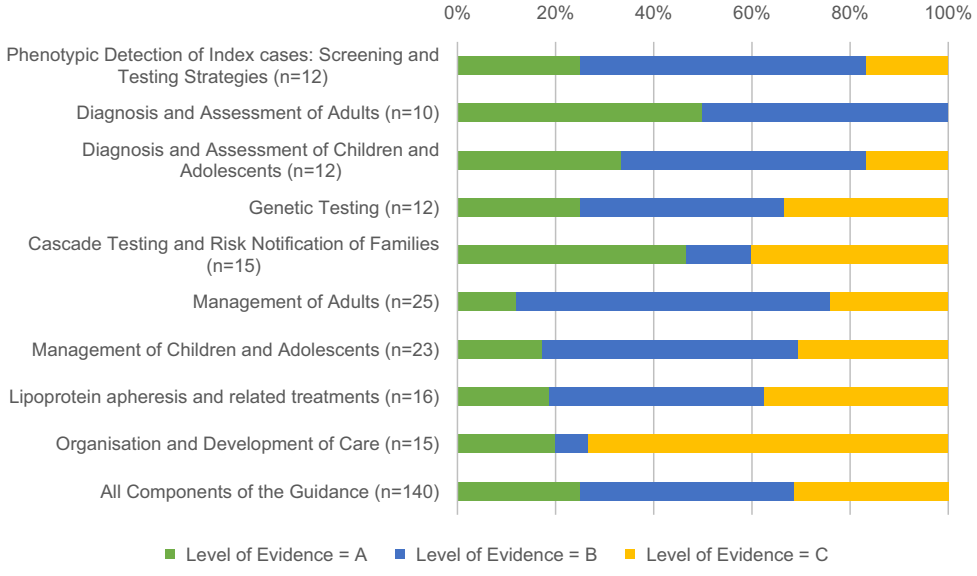
[c]Argument from first principles were employed for Statements 4.10, 5.4, 5.5, 5.6, 5.15, 9.7 and 9.10 (see Supplementary Material).

Appendix C. Distributions of classes of recommendation and levels of evidence for each major component of the guidance on FH.[a,b]

Classes of Recommendation:



Levels of Evidence:



[a]The percentages refer to the aggregate of all the statements contributing to each component of the guidance shown in Tables 1 to 9; numbers in brackets refer to the number of individual recommendations for each component.

[b]The published works used as evidence for recommendations are listed and referenced in the Supplementary Material.

Appendix D. The Dutch Lipid Clinic Network criteria for making the phenotypic diagnosis of FH in adult index cases.[a,b]

Criteria	Score
Section 1: Family history	
First degree relative with known premature coronary and/or vascular disease (men aged <55 yr, women aged <60 yr)	1
OR First degree relative with known LDL-cholesterol above the 95th percentile for age and gender	
First degree relative with tendinous xanthomata and/or arcus cornealis	2
OR Children aged <18 yr with LDL-cholesterol above the 95th percentile for age and gender	
Section 2: Clinical history	
Patients with premature coronary artery disease (men aged <55 yr, women aged <60 yr)	2
Patients with premature cerebral or peripheral vascular disease (men aged <55 yr, women aged <60 yr)	1
Section 3: Physical examination	
Tendinous xanthomata	6
Arcus cornealis before 45 yr of age	4
Section 3: Biochemical results	
LDL-cholesterol (mmol/L)[d]	
LDL-cholesterol ≥8.5[e]	8
LDL-cholesterol 6.5–8.4[e]	5
LDL-cholesterol 5.0–6.4[e]	3
LDL-cholesterol 4.0–4.9[e]	1
Diagnosis	**Total Score[c]**
Definite FH	>8
Probable FH	6-8
Possible FH	3-5
Unlikely FH	<3

[a]For online use, please access the FH Australasia Network calculator at https://www.athero.org.au/fh/calculator/.

[b]These criteria should not be used to diagnose FH in children or adolescents (see 3.5 in Table 3).

[c]Note that only the highest score in each section is chosen to add up to the total score, to a maximum of 18.

[d]If pre-treatment LDL-cholesterol is not available, use the FH Australasia Network's online calculator (https://www.athero.org.au/fh/calculator/) to derive LDL-cholesterol by adjusting value for cholesterol-lowering medication.

[e]To convert LDL-cholesterol from mmol/L to mg/dL, multiply by 38.67.

Appendix E. Lifestyle factors, clinical conditions and drugs that may increase plasma LDL-cholesterol concentrations.

Lifestyle factors
- Excess energy intake
- High saturated fat diet
- High trans-fat diet
- Weight gain
- Physical inactivity

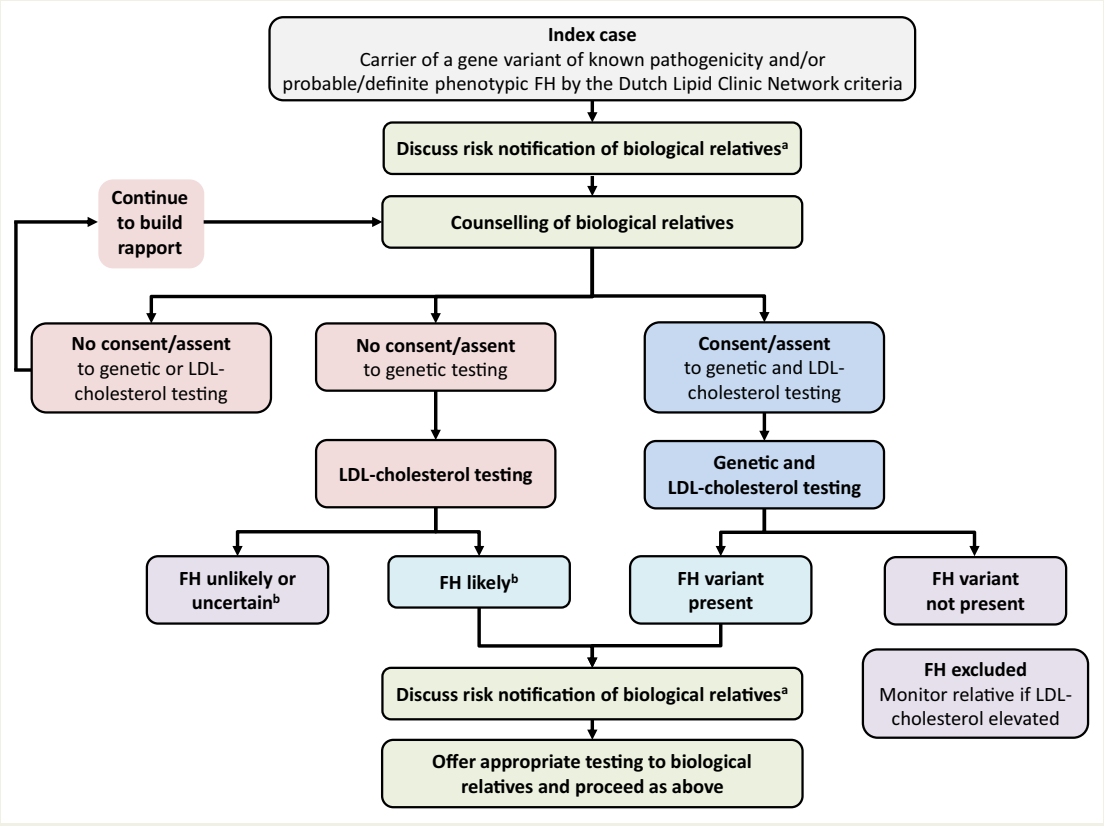
Clinical conditions
- Chronic kidney disease
- Nephrotic syndrome
- Obstructive liver disease
- Human immunodeficiency virus infection
- Systemic lupus erythematosus
- Hypothyroidism
- Pregnancy
- Polycystic ovary syndrome
- Anorexia nervosa
- Menopause

Drugs
- Some progestins (norethindrone)
- Anabolic steroids
- Danazol
- Isotretinoin
- Immunosuppressives (cyclosporine)
- Amiodarone
- Thiazide diuretics
- Glucocorticoids
- Thiazolidinediones (rosiglitazone)
- Fibric acids (in severe hypertriglyceridaemia)
- Omega-3 fatty acids (in severe hypertriglyceridaemia)

For further information, see the FH Australasia Network (https://www.athero.org.au/fh/health-professionals/secondary-causes-of-hypercholesterolaemia/) and Heart UK (https://www.heartuk.org.uk/genetic-conditions/secondary-hyperlipidaemia) websites.

Adapted from Jacobson et al. (2015) [46].

Appendix F. Process for cascade testing of biological relatives of an individual with confirmed FH.



[a]Consistent with relevant local legislation and institutional guidelines
[b]According to age- and gender-specific plasma LDL-cholesterol concentrations published by Starr et al. [76] (see Appendix G).
Abbreviations: FH, familial hypercholesterolaemia; LDL, low density lipoproteins
Adapted from Watts et al. (2011) [17].

Appendix G. Plasma low density lipoproteins (LDL)-cholesterol concentrations and thresholds (mmol/L)[a], based on age and gender, for making a diagnosis of familial hypercholesterolaemia (FH) during cascade testing of first-degree relatives of a patient with FH.

MALE

Age					
0 to 14	15 to 24	25 to 34	35 to 44	45 to 54	55 and older
5.5	5.5	5.5	5.5	5.5	5.5
5.4	5.4	5.4	5.4	5.4	5.4
5.3	5.3	5.3	5.3	5.3	5.3
5.2	5.2	5.2	5.2	5.2	5.2
5.1	5.1	5.1	5.1	5.1	5.1
5.0	5.0	5.0	5.0	5.0	5.0
4.9	4.9	4.9	4.9	4.9	4.9
4.8	4.8	4.8	4.8	4.8	4.8
4.7	4.7	4.7	4.7	4.7	4.7
4.6	4.6	4.6	4.6	4.6	4.6
4.5	4.5	4.5	4.5	4.5	4.5
4.4	4.4	4.4	4.4	4.4	4.4
4.3	4.3	4.3	4.3	4.3	4.3
4.2	4.2	4.2	4.2	4.2	4.2
4.1	4.1	4.1	4.1	4.1	4.1
4.0	4.0	4.0	4.0	4.0	4.0
3.9	3.9	3.9	3.9	3.9	3.9
3.8	3.8	3.8	3.8	3.8	3.8
3.7	3.7	3.7	3.7	3.7	3.7
3.6	3.6	3.6	3.6	3.6	3.6
3.5	3.5	3.5	3.5	3.5	3.5
3.4	3.4	3.4	3.4	3.4	3.4
3.3	3.3	3.3	3.3	3.3	3.3
3.2	3.2	3.2	3.2	3.2	3.2
3.1	3.1	3.1	3.1	3.1	3.1
3.0	3.0	3.0	3.0	3.0	3.0

FEMALE

Age					
0 to 14	15 to 24	25 to 34	35 to 44	45 to 54	55 and older
5.5	5.5	5.5	5.5	5.5	5.5
5.4	5.4	5.4	5.4	5.4	5.4
5.3	5.3	5.3	5.3	5.3	5.3
5.2	5.2	5.2	5.2	5.2	5.2
5.1	5.1	5.1	5.1	5.1	5.1
5.0	5.0	5.0	5.0	5.0	5.0
4.9	4.9	4.9	4.9	4.9	4.9
4.8	4.8	4.8	4.8	4.8	4.8
4.7	4.7	4.7	4.7	4.7	4.7
4.6	4.6	4.6	4.6	4.6	4.6
4.5	4.5	4.5	4.5	4.5	4.5
4.4	4.4	4.4	4.4	4.4	4.4
4.3	4.3	4.3	4.3	4.3	4.3
4.2	4.2	4.2	4.2	4.2	4.2
4.1	4.1	4.1	4.1	4.1	4.1
4.0	4.0	4.0	4.0	4.0	4.0
3.9	3.9	3.9	3.9	3.9	3.9
3.8	3.8	3.8	3.8	3.8	3.8
3.7	3.7	3.7	3.7	3.7	3.7
3.6	3.6	3.6	3.6	3.6	3.6
3.5	3.5	3.5	3.5	3.5	3.5
3.4	3.4	3.4	3.4	3.4	3.4
3.3	3.3	3.3	3.3	3.3	3.3
3.2	3.2	3.2	3.2	3.2	3.2
3.1	3.1	3.1	3.1	3.1	3.1
3.0	3.0	3.0	3.0	3.0	3.0

Colour	Likelihood of FH
	Likely
	Uncertain
	Unlikely

[a]To convert LDL-cholesterol from mmol/L to mg/dL, multiply mmol/L by 38.67.

Adapted from Starr et al. (2008) [76].

Appendix H. Selected organisations and related online resources for health care providers managing patients with familial hypercholesterolaemia (FH).

Organisation	Web address	Description
National Heart Foundation.	www.heartfoundation.org.au	Leading Australian charity that provides resources for health professionals and the community on all aspects of primary and secondary prevention of cardiovascular disease.
FH Australasia Network.	www.athero.org.au/fh	Network of clinicians and scientists from across Australia. Activities include the development of management guidelines, information sessions for clinicians, the establishment of various services around the country and a national registry.
FH Family Support Group.	www.fhfamilysupportgroup.websyte.com.au	Website of the first support group in Australia for families with familial hypercholesterolaemia (FH); provides relevant information to support families, communication and support services.
Centre for Genetics Education.	www.genetics.edu.au	Provides genetic educational resources for individuals and families affected by genetic conditions and also provides education and training in genetics and genomics for health care professionals.
Australian Genomics Health Alliance.	www.genomicsinfo.org.au	National body that funds and conducts research to build evidence to inform the integration of genomic medicine into mainstream health care.
FH Europe.	www.fheurope.org	Leading charity that focusses on sharing information and best practice across Europe, working with experts to focus topics of interest to the patients and families and support the development of newer or smaller patient groups.
British Heart Foundation.	www.bhf.org.uk	Leading British foundation that provides resources for health professionals and patients, including informative videos on a wide spectrum of conditions and risk factors.
Heart UK - The Cholesterol Charity.	www.heartuk.org.uk	Leading UK cholesterol charity that provides resources for health professionals, patients and families on all aspects of the detection and management of FH.
Wales FH Testing Service.	www.fhwales.co.uk	Exemplar FH service in Wales that provides useful information and resources for clinical practice.
Public Health Genomics Foundation.	www.phgfoundation.org	International foundation that publishes reports on the role of advances in genomics in health care; has a document on services for inherited cardiovascular conditions.
The FH Foundation.	www.thefhfoundation.org	Patient-centred US organisation dedicated to FH research, advocacy and education.
National Lipids Association (NLA).	www.lipid.org	US based multidisciplinary 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 NLA in the US.
Preventive Cardiovascular Nurses Association.	www.pcna.net	Leading nursing organisation dedicated to preventing and managing cardiovascular disease.