





## POSITION PAPER

# Integrated guidance to enhance the care of children and adolescents with familial hypercholesterolaemia: Practical advice for the community clinician

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Familial hypercholesterolaemia (FH) is a highly penetrant monogenic disorder present from birth that markedly elevates plasma low-density lipoprotein (LDL)-cholesterol (LDL-C) concentration and, if untreated, leads to premature atherosclerosis and coronary artery disease (CAD). At a prevalence of 1:250 individuals, with over 90% undiagnosed, recent estimates suggest that there are approximately 22 000 children and adolescents with FH in Australia and New Zealand. However, the overwhelming majority remain undetected and inadequately treated until adulthood or after their first cardiac event. The guidance in this paper aims to increase awareness about paediatric FH and provide practical advice for the diagnosis and management of FH in children and adolescents. Recommendations are given on the detection, diagnosis, assessment and management of FH in children and adolescents. Recommendations are also made on genetic testing, including counselling and the potential for universal screening programmes. Practical guidance on management includes treatment of non-cholesterol risk factors, and safe and appropriate use of LDL-C lowering therapies, including statins, ezetimibe, PCSK9 inhibitors and lipoprotein apheresis. Models of care for FH need to be adapted to local and regional health care needs and available resources. Targeting the detection of FH as a priority in children and young adults has the potential to alter the natural history of atherosclerotic cardiovascular disease and recognise the promise of early detection for improving long-term health outcomes. A comprehensive implementation strategy, informed by further research, including assessments of cost-benefit, will be required to ensure that this new guidance benefits all families with or at risk of FH.

**Key words:** cardiovascular disease; familial hypercholesterolaemia; genetic testing; inherited cardiac disease; paediatrics.

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Familial hypercholesterolaemia (FH) is a common and highly penetrant monogenic disorder, present from birth, that markedly elevates plasma low-density lipoprotein (LDL)-cholesterol (LDL-C) concentration, leading to premature atherosclerosis and coronary artery disease (CAD).<sup>1,2</sup> A genetically driven entity that affects 1:200–1:250 Australians and New Zealanders of all ethnicities and ages,<sup>3</sup> in those with a personal or family history of early atherosclerotic cardiovascular disease (ASCVD) the prevalence is even higher, up to 1:7.<sup>4</sup> Targeting the detection of FH as a priority in children and the young has the opportunity to have the greatest impact on the prevention of ASCVD.<sup>5–7</sup>

Based on recent estimates,<sup>8,9</sup> there may be as many as 20 000 children and adolescents with FH in Australia and 1400 in New Zealand. However, an overwhelming majority, up to 90%<sup>9</sup> of those affected remain undetected and therefore inadequately treated until adulthood or after their first cardiac event. This lack of individual recognition represents a public health emergency that deserves focused preventative health measures.<sup>10</sup> By increasing our understanding and recognition of paediatric FH, we have the opportunity to realise the significant public health and individual family impact of early detection and prevention of ASCVD.<sup>1,11,12</sup> Cascade screening and universal screening programmes have the power to cost-effectively reduce the burden of preventable cardiovascular disease in these high-risk populations.<sup>7,11–19</sup>

We present a practical guide for interpreting and implementing the FH guidelines for children and adolescents for general practitioners and paediatric specialists across Australia based on multi-disciplinary and shared-care. The recommendations in this article focus on Heterozygous FH (HeFH), which is caused by a single variant in a gene causing FH (monoallelic), with a complementary

discussion of Homozygous FH (HoFH), which is caused by two variants *in trans* (i.e., two genetic variants (or the same genetic variant) being present on both the maternal and paternal allele (compared to *in cis* where the variants are both on the same allele, either maternal or paternal)) in a gene causing FH (biallelic: may be homozygous with two copies of the same variant or compound heterozygous with two different variants on the maternal and paternal alleles). These recommendations are compatible with a contemporary global call to action on FH in childhood.<sup>20</sup> This extract provides key recommendations with their class (CoR) and level of evidence (LoE), as described in Appendix I. The full guidance, produced by the FH Australasia Network Consensus Working Group, is available in *Heart, Lung and Circulation*.<sup>21</sup>

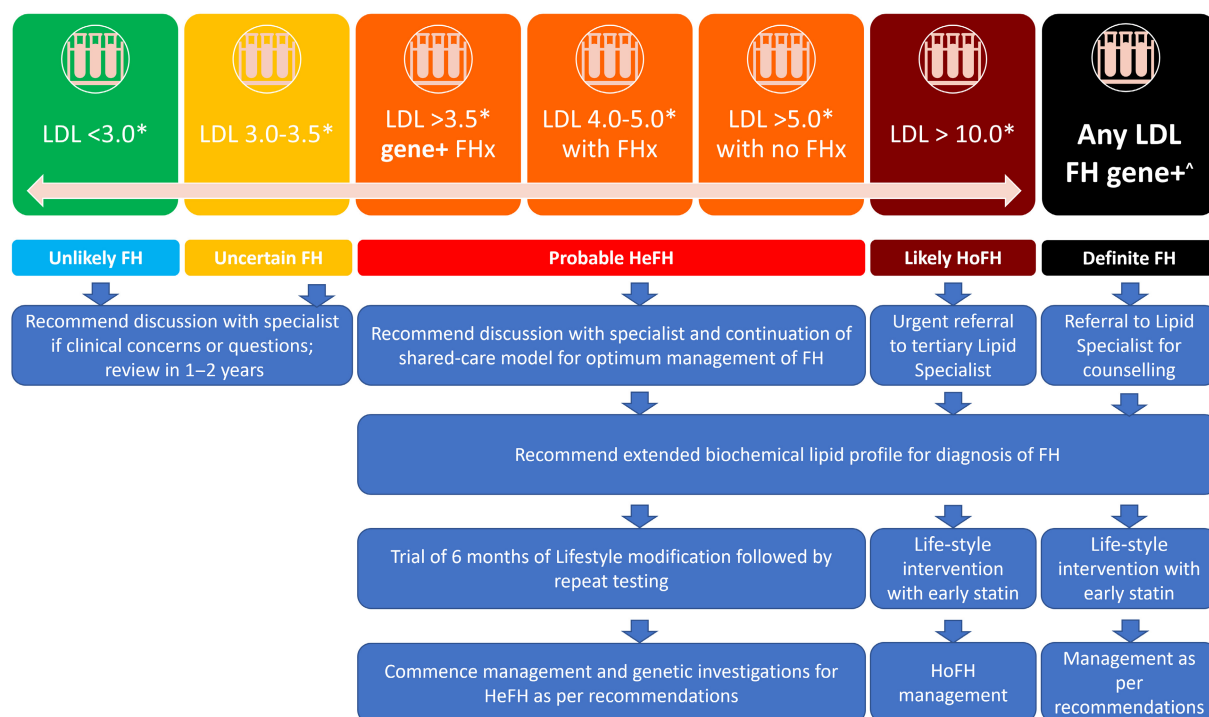
## Diagnosis and Assessment of Children

### Context and perspective

Recommendations for the early diagnosis and assessment for children and adolescents with suspected FH are provided in Table 1. The rationale for early diagnosis, assessment and screening in children is related to the cumulative lifetime burden of elevated LDL-C in individuals with FH, which starts to accrue in childhood.<sup>1,6</sup> The biggest gap in the care of individuals with FH is the early detection and treatment of children before ASCVD develops.<sup>23</sup> Several strategies that should be considered for detecting index cases of FH include selective, opportunistic and universal screening.<sup>14,24,25</sup> Selective and opportunistic screening should be undertaken in children who present to health-care services for related or unrelated reasons, whilst universal screening,

**Table 1** Phenotypic (clinical) detection and assessment of index cases: screening and testing strategies (Adapted from Watts *et al.*,<sup>21</sup> with permission.)

	Class	Level
1. Testing of children with suspected HeFH should be considered between the ages of 5 and 10 years using phenotypic (clinical) and genotypic strategies.	Moderate	Moderate
2. Testing of children with suspected HoFH can be considered as soon as the risk is recognised, ideally before age 2, and may be best supported by universal screening programmes.	Strong	Moderate
3. A probable diagnosis of FH should be considered in those with:	Moderate	Moderate
a) LDL-C of >5.0 mmol/L in the absence of parental history of hypercholesterolaemia or premature ASCVD;		
b) LDL-C of 4.0 to 5.0 mmol/L with parental history of hypercholesterolaemia or premature ASCVD; or		
c) LDL-C of >3.5 mmol/L with a parent with a pathogenic or likely pathogenic gene variant		
Age-dependent normal ranges can be seen in Figure 3 – this should be based on at least two fasting samples.		
4. The Dutch Lipid Clinic Network (DLCN) criteria should not be used in children and adolescents.	Strong	High
5. Genetic testing should be offered to diagnose children after a pathogenic or likely pathogenic gene variant has been identified in a parent or first-degree relative.	Strong	Moderate
6. Genetic testing of children, as potential index cases, should be considered when parents are unknown or deceased, or if specifically required to access special therapies.	Moderate	Moderate
7. Children and adolescents with HeFH should ideally be reviewed by a paediatric specialist with expertise in lipidology and access to multi-disciplinary services	Strong	Low
8. Children and adolescents with HoFH 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.	Strong	High
9. Children should be risk stratified according to other ASCVD risk factors, family history of premature ASCVD and level of LDL-C and Lip(a) at diagnosis, which should collectively guide clinical management.	Strong	Moderate
10. In children and adolescents with HeFH, carotid ultrasonography may be considered to assess ASCVD risk	Weak	Moderate
11. Universal screening, based on a plasma LDL-C level >3.5 mmol/L, should be considered before puberty (preferable between 1 and 2 years of age, coinciding with childhood immunisation) to initially detect children with FH.	Moderate	Moderate



**Fig. 1** Summary of overall assessment and initial management of FH. HeFH, heterozygous FH; HoFH, homozygous FH. \*On repeated testing including at least two or more fasting measurements. ^Molecular diagnosis of FH in childhood is confirmed with either a pathogenic or likely pathogenic variant detected in a gene with a known gene-disease association with FH, regardless of the patient's LDL.

based on a plasma LDL-C level  $>3.5$  mmol/L, should be considered in all children before puberty to increase the detection of FH prior to the development of ASCVD.<sup>1,6</sup> A biochemical diagnosis of probable FH is made with an LDL-C of  $>5.0$  mmol/L in the absence of parental history of hypercholesterolaemia or premature ASCVD; LDL-C of 4.0–5.0 mmol/L with parental history of hypercholesterolaemia or premature ASCVD; or LDL-C of  $>3.5$  mmol/L with a parent with a pathogenic or likely pathogenic gene variant. As the LDL-C levels increases, the probability of HoFH increases as well as the need to consider the rarer dyslipidemias (Fig. 1). Some organisations advocate for routine LDL-C measurement between age 1 and 2 years to coincide with childhood immunisation, to maximise the early detection and intervention rates.<sup>12–14</sup>

A molecular diagnosis of FH in childhood is confirmed with either a pathogenic or likely pathogenic variant detected in a gene with a known gene-disease association with FH, regardless of the patient's LDL. In the absence of a molecular diagnosis, clinical diagnosis of FH in childhood requires two or more fasting LDL-C measurements, including assessment after intensive life-style modification, together with exclusion of secondary causes of hypercholesterolaemia, including hypothyroidism, diabetes mellitus, renal disease, nephrotic syndrome, liver disease and medications (see full list in Appendix III).<sup>2</sup> Unlike adults, the Dutch Lipid Clinic Network criteria should not form part of the diagnostic assessment for children and adolescents with suspected FH.<sup>5,6,26</sup> This is because the examination and investigation findings that inform the DLCN score are not reliably present

in the younger age group.<sup>5,6,26</sup> Typical examination findings in individuals with FH include xanthomas, or patches of yellow cholesterol build-up, which increase with age. These typically occur around the eyelids and within the tendons of the elbows, hands, knees and feet.<sup>27–30</sup> Similar build-up in the eyes results in arcus cornealis.<sup>27–30</sup> In individuals with HoFH, these changes may be seen in childhood and adolescence, particularly with ultrasound of the achilles tendon<sup>6,29,31</sup>; however, in individuals with HeFH, these changes are not typically apparent until young adulthood, in the late 20s or later.<sup>27–30,32</sup> It is worth noting that calcific aortic valve stenosis may be a presenting feature in HoFH,<sup>32</sup> although it typically presents in older age groups. Assessment by a paediatric cardiologist is recommended as part of the assessment and management of both HeFH and HoFH.<sup>2,5</sup>

The presence of a family history of early onset or premature ASCVD increases the diagnostic suspicion for FH.<sup>2,4,29,33,34</sup> In this context, premature ASCVD refers to CAD occurring at age 55 years or younger in males and age 65 years or younger in females.<sup>2</sup> In some cases, children or adolescents may present as relatives (usually children) of an index case with a known genetic variant in a gene that causes FH.

Observational studies support the proactive treatment of FH beginning in childhood, as earlier intervention reduces the rate of accumulation of the lifetime of cholesterol burden and therefore delays onset of ASCVD – there is an adage the earlier, the better.<sup>6,35,36</sup> This proactive treatment may begin following clinical diagnosis in a child with elevated LDL-C, or presymptomatic

diagnosis following cascade testing from an affected parent with a known genetic variant in a gene that causes FH. Long-term follow-up of children with FH with relatively normal LDL-C at diagnosis is recommended.<sup>36</sup> As in adults, risk stratification enables personalised treatment strategies appropriate for their individual circumstances.<sup>37</sup> Consistent with international recommendations, children and adolescents with HeFH should preferably be reviewed by a paediatric specialist with expertise in lipidology and access to multi-disciplinary services.<sup>6,26</sup> Initial blood tests should include a fasting lipid profile but in the setting of a probable case, extended testing including a full blood count, electrolytes, urea and creatinine, liver function tests, C-reactive protein, creatine kinase, fasting lipid profile including triglycerides, thyroid function testing (TSH/FT4), ApoA, ApoB and Lipoprotein(a) should be done.<sup>6,29,38</sup>

A summary of management advice for children and adolescents with suspected FH is provided in Figure 1, whilst the variation in biochemical presentation, cardiovascular risk and typical age of onset of ASCVD is illustrated in Figure 2. Figure 3 demonstrates age-dependent normal values for LDL-C for phenotypic diagnosis and screening for FH and may assist with triaging risk and determination of referrals. Consider other rare dyslipidaemias if the clinical features, history and examination are atypical. A detailed discussion of this rare group of conditions is beyond the scope of this article.

## Genetic Testing

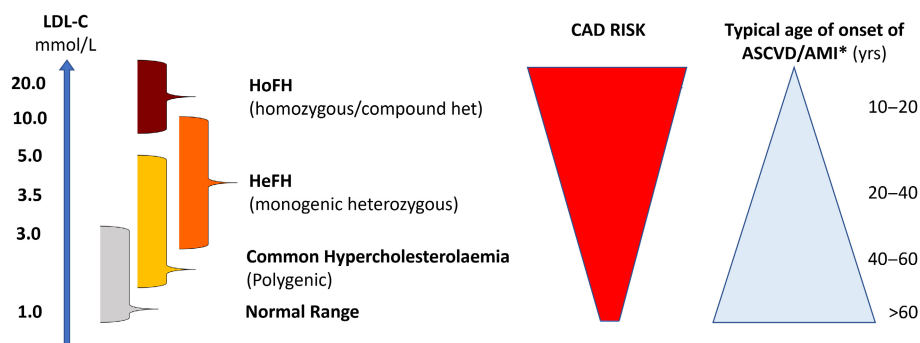
Diagnostic and variant-specific genetic testing (i.e., genetic testing for a known familial variant) for a broad range of heritable cardiovascular diseases are now recommended in paediatric patients.<sup>39</sup> Recommendations for genetic testing and genetic counselling for children and adolescents with suspected FH are provided in Table 2. Diagnostic genetic testing (i.e., genetic testing of a panel of genes in a new proband; also known as a new variant search, or new variant screen) and counselling for FH should ideally be offered to all children and adolescent index cases who have a probable/definite clinical suspicion of FH or a family history suggestive of FH with persistently raised cholesterol levels and may be considered in other clinical contexts.

An estimated 70%–95% of FH results from a heterozygous pathogenic variant in one of three genes (*APOB*, *LDLR* and *PCSK9*).<sup>40</sup> Additional genes that have been associated with inherited dyslipidaemias may be included by some genetic laboratories as part of an extended testing panel; clinical correlation

and referral to a clinical geneticist is recommended if a genetic variant is detected in one of these genes.<sup>1,17</sup> In the Australian context, a Medicare Benefit Schedule (MBS) Item Number (73352/73353) is available for subsidised genetic testing in specific clinical contexts for genetic variants in at least *APOB*, *LDLR* and *PCSK9* (Fig. 4), with other genes at the discretion of the pathology service. However, children with suspected FH are only eligible for MBS funded testing if LDL-C  $\geq 6.5$  mmol/L as criteria b(i) and b(iii) are generally not applicable in the paediatric population. Children will also be eligible for MBS funded testing in the case of cascade testing for a known familial variant. Public clinical genetics services in a child's local state can provide advice about eligibility for publicly (non-MBS) funded genetic testing, and self-funded testing may be an option for some families. It is important to note that a negative result from genetic testing is best viewed as 'uninformative' as it does not exclude a diagnosis of FH, as the individual may have an undetected genetic variant.<sup>5,33</sup> In all cases, genetic testing may be expanded to include genes that cause both FH and other familial dyslipidaemias depending on the clinical context.

Variant-specific genetic testing is more cost-effective than diagnostic testing<sup>11,41</sup> and should be employed to screen family members after a pathogenic, or likely pathogenic, gene variant has been identified in the family. If a pathogenic variant is identified and cascade screening offered to at risk children, then a negative cascade result can release a child from a lifetime of clinical screening and the fear of premature ASCVD, placing them instead at general population risk, with healthy life-style management and avoidance of secondary risk factors encouraged.<sup>4,41,42</sup> A confirmed genetic diagnosis can inform the use and choice of lipid lowering therapies (e.g. improved patient adherence to therapy, earlier initiation of therapy, more aggressive therapy or lower LDL-C targets), eligibility for clinical trials and aids with identification of family members at risk for the condition.<sup>4</sup>

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 and appropriate experience in counselling and consenting for genomic testing, including age- and culturally appropriate support, and in genetic test result interpretation.<sup>4,17,43</sup> Pre- and post-test genetic counselling should be offered to all at-risk family members as an integral component of cascade testing, and is of particular importance in children and young-adults to develop ongoing rapport and buy-in for long-term care.<sup>17</sup> It is important to create a safe space for the counselling, consenting and disclosure of genetic information given its



**Fig. 2** Variation in diagnostic groups, cardiac risk and presentations.\* Typical age of onset, without treatment/management.

**(a) MALES, age in years:**

0 to 14	15 to 24
> 4.0	> 4.0
3.9	3.9
3.8	3.8
3.7	3.7
3.6	3.6
3.5	3.5
3.4	3.4
3.3	3.3
3.2	3.2
3.1	3.1
3.0	3.0

**(b) FEMALES, age in years:**

0 to 14	15 to 24
> 4.0	> 4.0
3.9	3.9
3.8	3.8
3.7	3.7
3.6	3.6
3.5	3.5
3.4	3.4
3.3	3.3
3.2	3.2
3.1	3.1
3.0	3.0

Colour	Likelihood of FH
	Likely/Probable
	Uncertain
	Unlikely

**Fig. 3** (a and b) Age-dependent plasma LDL-C concentrations and thresholds (mmol/L) in first-degree relatives of an index case with FH. (Adapted from Starr *et al.*,<sup>22</sup> with permission.)

predictive nature and developmental significance. Older children and adolescents' benefit from feeling central to the consultation and decision-making process should be encouraged to be decision makers and provide assent together with their parents' consent for genetic testing. A child's developmental stage and maturity should be considered when including them in their consultation. Note that at-risk family members may include the parents or older siblings of a child or adolescent diagnosed with FH, and in this context the treating practitioner should ensure referral of the parents to an appropriate adult-based practitioner.<sup>5,6</sup>

Genetic testing and management for other inherited conditions that cause dyslipidaemia as part of the clinical presentation, including familial combined hyperlipidaemia (FCH), familial dysbetalipoproteinaemia, familial lipoprotein lipase deficiency, analphalipoproteinaemia (Tangier disease) and familial lecithin-cholesterol acyltransferase (LCAT) deficiency, are beyond the scope of these guidelines. Clinical correlation with genetic results

and referral to a clinical geneticist and other relevant specialists are strongly recommended.<sup>17,44</sup> In addition, up to 30% of patients clinically suspected to have monogenic FH demonstrate polygenic hypercholesterolemias.<sup>33</sup> Complex cases are best discussed with specialist colleagues.

If a universal screening programme was to be employed, this should be coupled with child to parent (reverse) cascade testing.<sup>6</sup> There is mounting evidence in support of multifaceted universal screening programmes both overseas,<sup>12,14,45,46</sup> and in the Australian context.<sup>18,19</sup>

### Important Points for Discussion as Part of Genetic Counselling in FH

Pre- and post-test counselling for suspected or confirmed FH is critical as part of the consultation and care of children and adolescents as well as their family. Where available,



**Table 2** Genetic testing and counselling for children and adolescents with suspected FH (Adapted from Watts *et al.*,<sup>21</sup> with permission.)

	Class	Level
1. 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 programme, or if specifically required to gain access to targeted therapies for FH.	Moderate	Moderate
2. 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	Strong	High
3. Cascade testing (testing of consenting biological relatives of an individual with confirmed 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	Strong	High
4. 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.	Strong	High
5. Pre- and post-test genetic counselling should be offered to all at risk family members as an integral component of cascade testing.	Strong	High
6. Universal screening of children should be coupled with child–parent (reverse) cascade testing.	Strong	Moderate
7. 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.	Strong	Low
8. 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.	Strong	Low
9. 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).	Strong	Moderate

counselling should involve a genetic counsellor together with follow-up in a timely manner to address coping and responses to diagnosis; however, we recognise there is a shortage of genetic counsellors in Australia and world-wide, especially in the primary care context. All staff involved in the care of

patients should have training in genetic counselling to best support the care and education of staff, families and the community. Box 1 describes common pre- and post-test counselling issues for consideration as part of the adolescent and family centred consultation.

## Medicare Benefits Schedule – Item 73352

### Please note MBS funding for familial hypercholesterolaemia covers:

Characterisation of germline variants causing familial hypercholesterolaemia (which must include the *LDLR*, *PCSK9* and *APOB* genes), requested by a specialist or consultant physician, for a patient:

- (a) for whom no familial mutation has been identified; and
- (b) who has any of the following:
  - (i) a Dutch Lipid Clinic Network score of at least 6;
  - (ii) an LDL-cholesterol level of at least 6.5 mmol/L in the absence of secondary causes;
  - (iii) an LDL-cholesterol level of between 5.0 and 6.5 mmol/L with signs of premature or ACSVD

Applicable only once per lifetime

## Medicare Benefits Schedule – Item 73353

Detection of a familial mutation for a patient who has a first- or second-degree relative with a documented pathogenic germline variant for familial hypercholesterolaemia

Applicable only once per lifetime

**Fig. 4** Australian Medicare Item Numbers for subsidised FH genetic testing.

**Box 1** Pre- and post-test counselling issues for consideration  
*Issues that may arise as part of pre-test counselling include*<sup>4,47</sup>:

- Grief/anger related to illness or loss of family members to premature ASCVD (if relevant)
- Risk of cardiovascular events
- Brief explanation of inheritance – typically autosomal dominant inheritance, 50% risk if parent is affected
- Potential risk to family members, siblings, current/future children
- Importance of open discussion and communication between all family members including children at a developmentally appropriate time and level
- Residual risk in the case of an uninformative genetic testing result (i.e. FH diagnosis not excluded)
- Potential future impact of a result on an ability to obtain certain types of insurance (including life and income protection insurance) above a certain threshold and current impact for adult family members<sup>48</sup>
- In Australia, genetic testing does not impact on a person's ability to obtain health insurance
- Potential impact of a result on access to certain funded medical therapies
- Personalised care and a results ability to assist with determination of treatment options and target levels

*Issues that may arise as part of post-test counselling issues include*<sup>4,47</sup>:

- Explanation of the type of result – pathogenic, likely pathogenic, variant of uncertain significance (VUS), uninformative result (when genetic testing does not identify a causative variant, however this does not exclude the presence of an undetected variant. In other words, an uninformative result does not rule out a diagnosis in a patient with a positive phenotype and/or family history)
- Further testing that may be required to clarify result
- Practical advice pertaining to the management of a patient
- Practical advice pertaining to screening and genetic testing for at risk family members
- Support after a positive pathogenic or likely pathogenic result
- Assisting patient and family to communicate results to health professionals and family members
- Discussion of reproductive risk and reproductive options especially for adolescent and young adults as part of transition to adult services
- Importance of emergency management plans and school-management plans
- Referral and enrolment in the Australian National FH Registry

## Management of FH in Children and Adolescents

Recommendations for the management of children and adolescents with suspected or proven FH are provided in Table 3. Management should be based on shared decision-making with parents and all children and adolescents, with a developmentally appropriate and inclusive approach.<sup>5,6,26,49,50</sup> In particular, barriers to treatment adherence and reduction or avoidance of secondary risk factors should be explored and reinforced.<sup>51</sup>

Telehealth may further reduce barriers for accessing specialist and primary care and facilitate improved integration into multi-disciplinary health-care systems.<sup>52</sup> A shared-care model with the family GP should be encouraged. Provision of contact details for support groups for patients and families may assist with improving the quality of care.

The concept of a healthy heart life-style should be introduced at an early age and should include<sup>5,6,8,26,44,49,50</sup>:

- eating a healthy diet (low in saturated and trans-fat and with/without plant sterols)
- doing regular physical activity
- being an appropriate weight (doctor will advise on this)
- not smoking
- avoiding alcohol
- maintaining social and emotional health

For some families, adopting a healthy heart life-style for all members of the family may improve management adherence and improve the health of all family members, including those without FH.<sup>5,6,8,26,44,49,50</sup> For children who require medication, a family routine for medication taking may enhance adherence for both children and affected adults.<sup>5,6,8,26,44,49,50</sup>

Statins are the first choice in medication and can reduce LDL cholesterol levels by up to 50% when using high-dose regimes,<sup>2,6,26,38</sup> but age-appropriate targets do not often necessitate high-dosing.<sup>2,6,26,38</sup> Additional medications may include cholesterol absorption inhibitors (Ezetimibe) and bile acid binding resins (compliance for this medication is often poor in children).<sup>2,6,26,38,53–56</sup>

In children and adolescents with HeFH, the initiation of statin treatment should be considered at age 8–10 years in both males and females. LDL-C targets in children and adolescents with HeFH need not be as intensive as in adults.<sup>6,26,38,57</sup> In children with HeFH between the ages of 8 and 10 years on a suitable diet, a treatment target of low-density lipoprotein (LDL)-cholesterol <4.0 mmol/L or a 30–40% reduction in LDL-C may be considered.<sup>6,26,38,57</sup> In children with HeFH older than 10 years on a suitable diet, a treatment target of LDL-C < 3.5 mmol/L or a 50% reduction in LDL-C may be considered.<sup>6,26,38,57</sup> 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.<sup>5,6,26</sup> Earlier initiation of treatment with statins should be considered in FH patients with a particularly adverse family history of ASCVD or those children who have other major ASCVD risk factors. Earlier initiation of treatment is an enabler for enhancing life-long adherence to therapy,<sup>58</sup> and consideration of enablers and barriers to adherence should be considered when devising management plans together with patients and families.<sup>58,59</sup> In HoFH, treatment should begin as early as age 2 years.<sup>1,6,23,31</sup>

In children, licensed statins include pravastatin, fluvastatin and simvastatin and secondarily atorvastatin and rosuvastatin. Ezetimibe is licensed from age 10 years but may be used at younger ages as recommended by specialist lipidology colleagues.<sup>5,6,17,26</sup> The use of maximal doses of potent statins and ezetimibe should be considered in HoFH children as early as possible, ideally by the age of 2 years.<sup>1,6,29,60</sup> The use of a proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitor may be considered in HeFH and should be considered as essential to the care in

**Table 3** Management recommendations for children and adolescents with suspected or proven FH (Adapted from Watts *et al.*<sup>21</sup> with permission.)

	Class	Level
1. 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.	Strong	Moderate
2. All patients and families with FH should be offered counselling on life-style 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); life-style counselling on primordial prevention (i.e. the development of risk factors) is particularly important.	Strong	Moderate
3. In children and adolescents with HeFH, the initiation of statin treatment should be considered at age 8 to 10 years in both males and females; plasma LDL-C targets in children and adolescents need not be as intensive as in adults	Moderate	Moderate
4. Earlier initiation of treatment with statins should be considered in HeFH patients with a particularly adverse family history of atherosclerotic cardiovascular disease (ASCVD) (related specifically to FH) or who have other major ASCVD risk factors.	Moderate	Moderate
5. In children with HeFH between the ages of 8 and 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-C may be considered.	Weak	Low
6. In children with HeFH older than 10 years on a suitable diet, a treatment target of LDL-C <3.5 mmol/L or a 50% reduction in LDL-C may be considered.	Weak	Low
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	Strong	High
8. Statins licensed in Australia for use in this age group should be employed: these include pravastatin, fluvastatin and simvastatin; ezetimibe is licensed from the age of 10 years and should be used accordingly. Atorvastatin and rosuvastatin should be considered as options according to clinical indications.	Strong	High
9. The use of a proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitor may be considered in HeFH according to clinical indications and shared decision-making, noting that experience with and long-term safety of this drug class are limited in this age group	Weak	Moderate
10. The use of maximal doses of potent statins and ezetimibe should be considered in HoFH children as early as possible, ideally by the age of 2 years	Moderate	Moderate
11. In children and adolescents with HoFH, treatment should commence as soon as possible after diagnosis: the LDL-C target should be similar to adults, which may require addition of a PCSK9 inhibitor to a statin and ezetimibe, as well as the use of lipoprotein apheresis.	Strong	Moderate
12. Lomitapide and evinacumab may be considered, via special access or compassionate use schemes, in all patients with HoFH and rapidly progressive ASCVD, as adjunctive treatments to diet and other drugs, to further lower plasma LDL-C, particularly if lipoprotein apheresis is not feasible.	Weak	Low
13. Lipoprotein apheresis should be considered in children with HoFH or severe HeFH by the age of 5 years and no later than 8 years, in all patients who cannot achieve LDL-C targets despite maximally tolerated drug therapy, including PCSK9 inhibitors.	Moderate	Moderate
14. 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-C in homozygous FH on lipoprotein apheresis, particularly in patients who have two LDL-receptor null alleles.	Weak	Low
15. Orthotopic liver transplantation should be considered for younger patients with HoFH who have rapid progression of ASCVD or aortic stenosis, who cannot tolerate lipoprotein apheresis, or whose plasma LDL-C cannot be adequately lowered with diet, drug treatment and lipoprotein apheresis	Moderate	Low

HoFH 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 with trials describing efficacy and safety currently updating clinical practice.<sup>6,61–65</sup>

An aid to treatment initiation and management for both HeFH and HoFH is described in Figure 5, whilst the recommended target treatment levels are summarised in Figure 6. Figure 7 demonstrates evidenced-based typical response to therapy by treatment class and intensity. Figure 8 shows the natural history and impact of intervention on LDL cholesterol burden in individuals with or without FH as a function of the age of initiation of statin therapy.

## Monitoring of Treatment Response

Recommendations for monitoring of treatment for children and adolescents with suspected or proven FH are provided in Table 4.

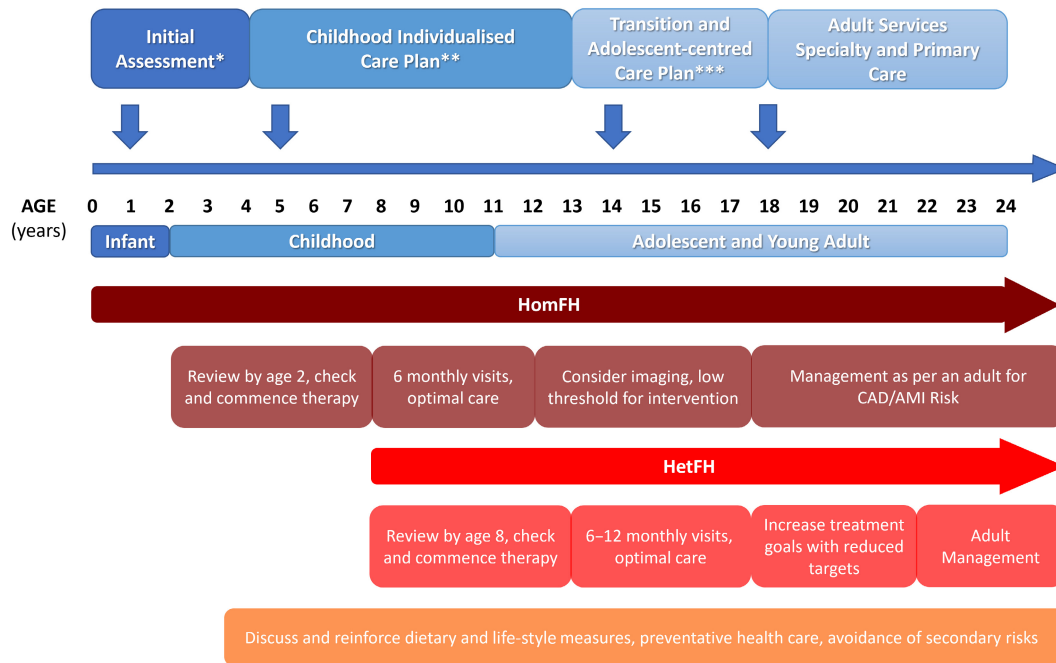
Recommended investigations are detailed in Figure 9 for both the first line or screening blood and imaging tests as well as ongoing testing of value.

## Tests

- Regular blood tests will monitor side effects and adherence to medication
- Carotid ultrasound measuring carotid intimal medial thickness (CIMT) and presence/progression of plaques may help to guide the intensity of treatment; however, it is not readily available in all centres.<sup>5,23,67,68</sup>

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.<sup>6,26,54,56,57,69–73</sup> Plasma levels of hepatic aminotransferases, creatine kinase, glucose and

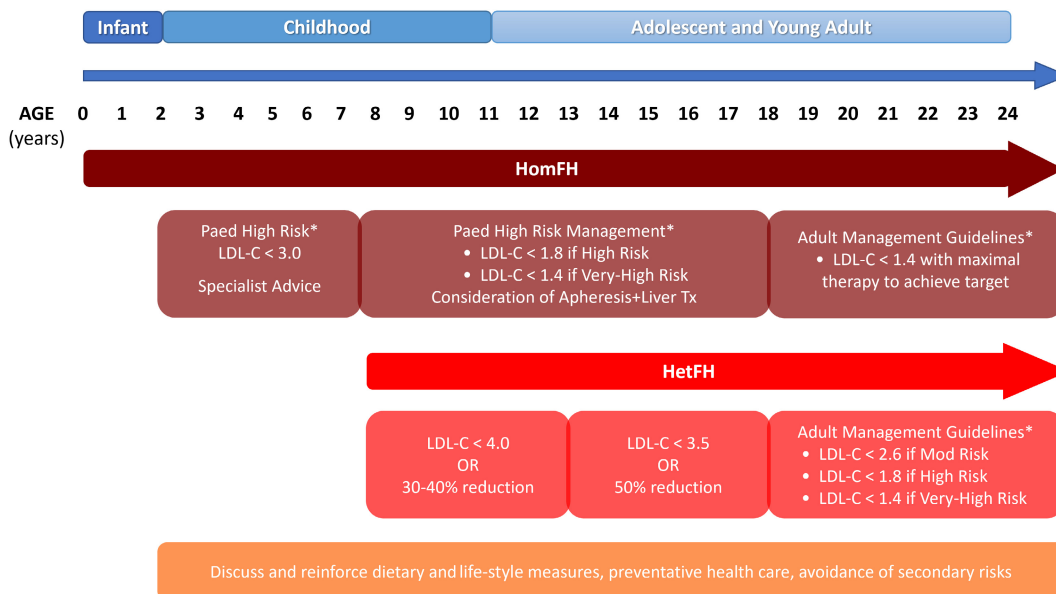




**Fig. 5** Treatment initiation and management journey. \*Initial assessment includes cascade testing, universal screening or incidental finding of raised LDL-C at any age less than 18 years. \*\*Individualised care plan should be shared with parents and GP and clearly sets out frequency of follow-up and repeat blood tests to monitor LDL, treatment side-effects and should be by a paediatric professional together with a lipid specialist. \*\*\*Transition and transition clinics require special consideration for supporting the adolescent to be a key part of their plan and care, support independence in a safe-space with tailored care, and begin discussions of care in the adult services.

creatinine should be measured before starting and dose titrating drug therapy.<sup>2,5</sup> All patients on statins should have hepatic aminotransferases monitored; creatine kinase should be measured

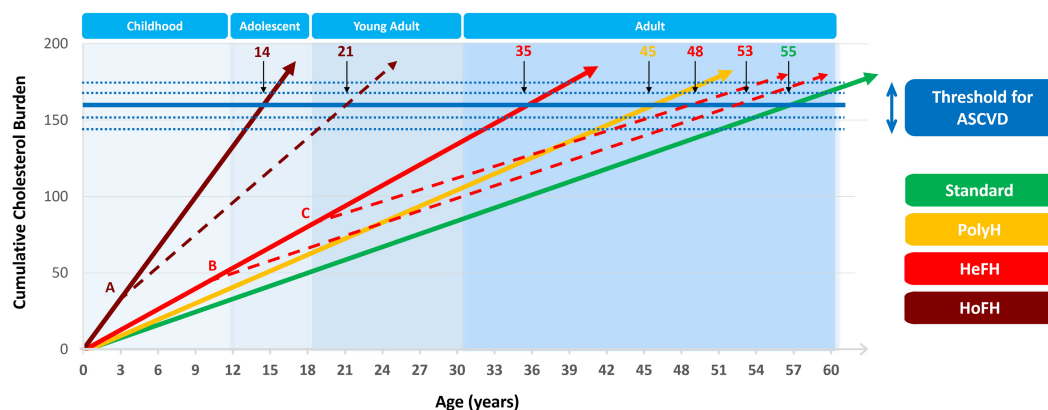
and compared to pre-treatment levels when musculoskeletal symptoms are reported; glucose should be monitored, particularly if there are risk factors for diabetes.<sup>2,5</sup> Monitoring of common



**Fig. 6** Treatment Targets for Paediatric Patients. \*In both HeFH and HoFH, target LDL-C levels should be considered with specialist advice and may be reduced in cases with significant family history of ASCVD or in those children who have other major ASCVD risk factors.

Intensity of Lipid Lowering Treatment	
Treatment	Expected average LDL-C reduction
Moderate-intensity statin	≈ 30%
High-intensity statin	≈ 50%
High-intensity statin + Ezetimibe	≈ 65%
PCSK9 inhibitor	≈ 60%
PCSK9 inhibitor + high-intensity statin	≈ 75%
PCSK9 inhibitor + high-intensity statin + Ezetimibe	≈ 85%

**Fig. 7** Treatment class – average intensity/response to therapy (Adapted from the ESC guidelines 2019<sup>2</sup> with permission.)



**Fig. 8** LDL cholesterol burden in individuals with or without FH as a function of the age of initiation of statin therapy. Standard = Population Risk including standard secondary risk factors; PolyH = Polygenic hypercholesterolaemia = High Risk non-FH populations with increased risk eg. Indian subcontinent with strong FHx of early ASCVD; HeFH = heterozygous FH; HoFH = homozygous FH. A indicates HoFH with treatment started age 2-3yo; B indicates HeFH with treatment started age 8-10yo; C indicates Het FH with treatment started age 18yo; — Solid line represents patient who is undiagnosed or untreated in that class; - - Dotted line represents patient who begins treatment prior to the onset of ASCVD at different ages; threshold for CAD/ASCVD is modified by secondary risk factors and family history: increased threshold if female, decreased threshold and earlier onset ASCVD if male, smoking, hypertension, diabetes, obesity, increased triglycerides, decreased HDL-C, increased Lipoprotein(a). (Adapted from Nordestgaard *et al.*,<sup>66</sup> based on data from Starr *et al.*,<sup>22</sup> with permission.)

**Table 4** Monitoring of treatment in children and adolescents with suspected or proven FH (Adapted from Watts *et al.*<sup>21</sup> with permission.)

	Class	Level
1. Fasting samples should be used to assess LDL-C responses to the initiation of and change in drug therapy, as well as to monitor LDL-C in patients with unstable plasma lipid profiles or elevated triglycerides	Strong	Moderate
2. Non-fasting samples are particularly convenient in children and should be considered for monitoring LDL-C in patients who are on stable drug therapy and do not have elevated triglycerides	Moderate	Low
3. 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	Strong	High
4. 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	Strong	Moderate
5. 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.	Strong	Moderate
	Moderate	Low

(Continues)

**Table 4** (Continued)

	Class	Level
6. Shared care between paediatric specialists and general practitioners (GPs) should be considered for managing well-controlled and lower complexity patients with HeFH.		
7. Management should focus on the nuclear or the immediate family, with at least an annual review of children; non-adherence should be addressed.	Strong	Low
8. 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.	Moderate	Low
9. In children and adolescents with HeFH, carotid ultrasonography (carried out in centres with relevant expertise) may be employed to monitor therapy, but its clinical value is not fully established.	Weak	Moderate
10. In children and adolescents with HoFH, computed tomography coronary angiography (CTCA), carotid ultrasonography (CIMT), 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.	Strong	Moderate

side effects including nausea, abdominal pain and diarrhoea are also important in children.<sup>2,5</sup>

Fasting samples should be used to assess LDL-C responses to the initiation of and change in drug therapy, as well as to monitor LDL-C in patients with unstable plasma lipid profiles or elevated triglycerides.<sup>74–76</sup> Non-fasting samples are particularly convenient in children and can be considered for monitoring LDL-C in patients who are on stable drug therapy and do not have elevated triglycerides.<sup>74–76</sup>

## Transition

Recommendations for transition and service development for adolescents with suspected or proven FH are provided in Table 5. 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.<sup>77</sup> Transition clinics require special consideration for supporting the adolescent to be a key part of their plan and care,

support independence in a safe-space with tailored care, and begin discussions of care in the adult services.<sup>51,77</sup> These strategies are particularly important to optimise adherence to medical therapy.<sup>51</sup> A typical model for a transitional care clinic may involve combined care with a paediatric lipid specialist together with a primary care physician or a paediatric and an adult lipid specialist and cardiologist.<sup>6</sup> Management should be based on shared decision-making with patients on an ongoing basis for ‘whole-of-life’ care.<sup>49,50</sup> In particular, barriers to treatment adherence and reduction or avoidance of secondary risk factors should be explored and reinforced at this pivotal juncture to improve outcomes in adulthood.<sup>51</sup>

If you have a patient with a new diagnosis of likely or definite FH, please refer them to the Australian National FH Registry. Details can be found at:

<https://www.athero.org.au/fh/patients/fh-registry/>

Pathology First Line (Screening)	Pathology Second Line (Diagnosis and Management)	Imaging First Line (Diagnosis)	Imaging Second Line (Management)	Imaging Third Line (Management)
FBE UEC LFT TFT  ----- Fasting Lipid Profile	FBE UEC LFT TFT CRP CK HbA1c  ----- Fasting Lipid Profile ApoB Lip(a)	Cardiology Review* - baseline ECHO - baseline ECG Ophthalmology Assessment*  *Recommended for HoFH; may be considered for HeFH	Carotid USS/CIMT* Ankle USS* (for tendon xanthoma)  *Recommended for HoFH; may be considered for HeFH	CTCA (HoFH)

**Fig. 9** Recommended Investigations.<sup>6,29,38,67</sup>

**Table 5** Transition and service development considerations for adolescents with suspected or proven FH (Adapted from Watts *et al.*<sup>21</sup> with permission.)

	Class	Level
1. 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.	Strong	Low
2. 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.	Strong	Low
3. Specialist care should have access to lipidology, cardiology, endocrinology, paediatric, genetic, imaging, transfusion medicine, nursing, dietetic, psychology, pharmacy practice, pathology and telehealth services.	Strong	Low
4. 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.	Strong	Low

## Service Development and Implementation Considerations

Health-care pathways should be developed to meet the needs of local, regional and remote communities,<sup>1</sup> 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. Each region will have individualised pathways and you should connect with local specialists to develop links to assist you with care of patients. Local specialists in lipidology can be found on the FH Australia website (see below).

Advocacy organisations and clinician support resources can be pivotal to the care of families, development of community and support during diagnosis and counselling.<sup>1</sup> Appendix II contains a further list of useful links for clinicians and families.

The implementation of multinational guidelines to prevent cardiovascular disease in clinical practice requires stakeholder engagement, awareness and promotion of organisational change.<sup>78</sup> These guidelines aim to empower health professionals and patients alike, by engaging primary and specialist clinicians and increasing knowledge of the detection and management of FH in the paediatric population.

### FH Family Support Group

<http://www.fhfamilysupportgroup.websyte.com.au>

Website of the first support group in Australia for families with FH; provides relevant information to support families, communication and support services.

### Facebook FH Support Group

[https://www.facebook.com/](https://www.facebook.com/FHAustralasiaNetworkandSupportGroup)

[FHAustralasiaNetworkandSupportGroup](https://www.facebook.com/FHAustralasiaNetworkandSupportGroup)

### Clinician Resources

<https://www.athero.org.au/fh/health-professionals/specialists-resources/>

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## Appendix I

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

The published works employed as evidence to support individual recommendations are specified in the Supplementary Material (Table 1, Table 2, Table 3, Table 4, Table 5, and References 1 to 148).

Classes of recommendations <sup>†</sup>	
Strong recommendation: There is high certainty based on the evidence that the net benefit is substantial <i>Wording: should be performed; can be trusted to guide practice</i>	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 <i>Wording: should be considered; can be trusted to guide practice in most situations</i>	Moderate = 2
Weak recommendation: There is at least moderate certainty based on the evidence that there is a small net benefit <i>Wording: may be considered; can be trusted to guide practice, but care should be taken in its application</i>	Weak = 3
Levels of evidence <sup>‡</sup>	
Highly certain about the estimate of effect; further research is unlikely to change our confidence in the estimate of effect <i>Bases: Randomised-controlled trials/meta-analyses/systematic reviews/good quality diagnostic studies</i>	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 <i>Bases: Good quality clinical or observational studies</i>	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 <i>Bases: Expert opinion based on clinical experience or argument from first principles*</i>	Low = C

<sup>†</sup>This system was based on the American Heart Association/American College of Cardiology<sup>79</sup> and the National Lipid Association<sup>80</sup> cholesterol guidelines.

<sup>‡</sup>This system was based on the American Heart Association/American College of Cardiology<sup>79</sup> and the National Lipid Association<sup>81</sup> cholesterol guidelines, and adapted from the original GRADE system of evidence rating,<sup>82</sup> which is in turn endorsed by the National Health and Medical Research Council Guidelines for Guidelines.<sup>83</sup>

The above systems for grading recommendations and evidence were agreed by consensus at workshops on the development of lipid position statements, held by the AAS in 2018, attended by members of the steering committee, members of the AAS Clinical Council and various contributors.

## Appendix II

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

Organisation	Web address	Description
National Heart Foundation	<a href="http://www.heartfoundation.org.au">http://www.heartfoundation.org.au</a>	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	<a href="http://www.athero.org.au/fh">http://www.athero.org.au/fh</a>	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	<a href="http://www.fhfamilysupportgroup.websyte.com.au">http://www.fhfamilysupportgroup.websyte.com.au</a>	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	<a href="http://www.genetics.edu.au">http://www.genetics.edu.au</a>	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.
FH Europe	<a href="http://www.fheurope.org">http://www.fheurope.org</a>	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.

Organisation	Web address	Description
Heart UK – The Cholesterol Charity	<a href="http://www.heartuk.org.uk">http://www.heartuk.org.uk</a>	Leading UK cholesterol charity that provides resources for health professionals, patients and families on all aspects of the detection and management of FH.
The FH Foundation	<a href="http://www.thefhfoundation.org">http://www.thefhfoundation.org</a>	Patient-centred US organisation dedicated to FH research, advocacy and education.
National Lipids Association (NLA)	<a href="http://www.lipid.org">http://www.lipid.org</a>	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	<a href="http://www.learnyourlipids.com">http://www.learnyourlipids.com</a>	Information for patients with dyslipidaemia, including FH, as provided by the foundation of the NLA in the United States.

## Appendix III

### Secondary Causes of Increased LDL-C

Life-style factors, clinical conditions and drugs that may increase plasma LDL-C concentrations.

Life-style factors	Excess energy intake
	High saturated fat diet
	High trans-fat diet
	Weight gain
Clinical conditions	Physical inactivity
	Chronic kidney disease
	Nephrotic syndrome
	Obstructive liver disease
	Human immunodeficiency virus infection
	Systemic lupus erythematosus
	Hypothyroidism
	Pregnancy
	Polycystic ovary syndrome
	Obesity
	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.*,<sup>80</sup> with permission.

## Appendix IV

### Specific at Risk Populations – Prevalence of FH in Select Populations

Population	Prevalence
General population (World)	1:250
General population (Australia)	1:200–250
French Canadian	1:270
Christian Lebanese	1:85
Tunisia	1:165
South African Afrikaners	1:72 to 1:100
South African Ashkenazi Jews	1:67
Japanese	1:900
Adapted from Austin <i>et al.</i> , <sup>84</sup> and Akioyamen <i>et al.</i> , <sup>3</sup> with permission.	