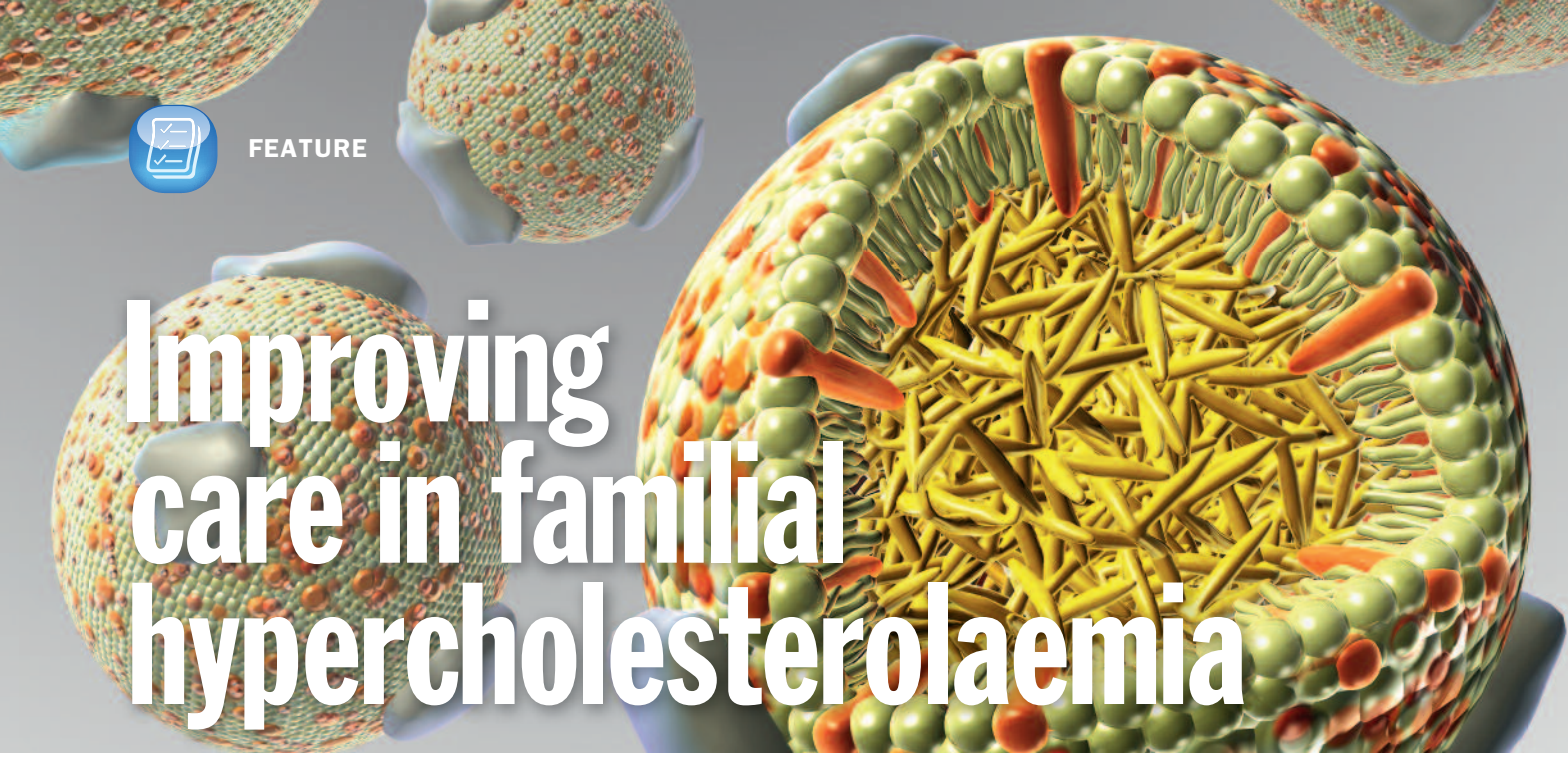

FEATURE

Improving care in familial hypercholesterolaemia

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Most people with FH in Australia and New Zealand are unrecognised and inadequately treated. To bridge this gap in coronary prevention, the FH Australasia Network has developed a model of care for patients with FH, focusing on detecting, diagnosing, assessing and managing index cases, as well as on risk notification and cascade screening of family members.

Familial hypercholesterolaemia (FH) is a condition that should be familiar to all health-care professionals involved in preventive medicine. FH is the most common and serious monogenic disorder of lipid metabolism that leads to premature coronary heart disease (CHD) due to accelerated atherosclerosis.[1,2] It is an autosomal co-dominantly inherited disorder caused primarily by mutations in the gene that encodes the LDL receptor; rarer mutations in the *apolipoprotein B-100* and *PCSK9* genes have similar consequences. A typical pedigree illustrating the phenotypic inheritance of FH is shown in Figure 1.

In FH, a defect in the LDL-receptor pathway decreases the clearance of LDL cholesterol (LDL-C) from plasma, resulting in an increase in the plasma concentration of total cholesterol and LDL-C.

The prevalence of FH is estimated to be at least one in 500 in the general population, and is much higher in communities subject to a 'founder gene effect'.[2,3] The therapeutic use of statins in routine clinical practice since about 1990 has markedly improved the prognosis of patients diagnosed with FH.[4] However, most cases of FH remain undetected or inadequately treated in our community.[5-7] To meet this medical need, the FH Australasia Network has developed a model of care for patients with FH, which is briefly summarised in this article.[8]

Key points

- **At least 45,000 people have FH in Australia and New Zealand, but most are unrecognised and inadequately treated.**
- **The FH Australasia Network has developed a model of care for patients with FH (summarised in this article) that focuses on detecting, diagnosing, assessing and managing index cases of FH, as well as risk notification and cascade screening of family members.**
- **Index cases of FH should be sought among adults with premature cardiovascular disease in different clinical settings, and all patients considered to have FH should be referred to a lipid disorders clinic for further assessment and institution of cascade screening.**
- **Not all patients with FH have the same risk of CHD; hence, risk stratification of patients determined by the presence of cardiovascular risk factors and a personal history of cardiovascular disease should be used to guide the intensity of medical management.**

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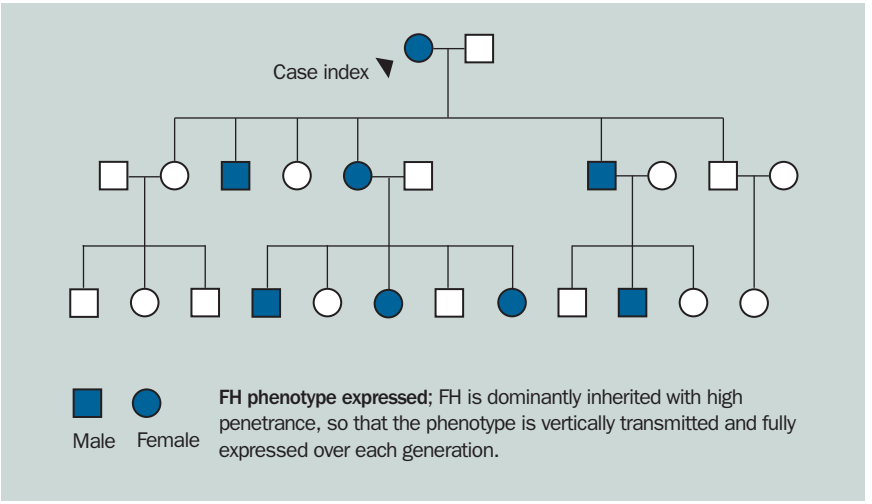


Figure 1. Pedigree depicting dominantly inherited phenotype in a family with heterozygous familial hypercholesterolaemia (FH).

Table 1. Dutch Lipid Clinic Network Criteria for establishing a diagnosis of familial hypercholesterolaemia (FH) in adults[8]

Feature	Score
Family history	
First-degree relative with known premature coronary and/or vascular disease (men <55 years, females <60 years) OR First-degree relative with known LDL-C above the 95th percentile for age and sex	1
First-degree relative with tendinous xanthomata and/or arcus cornealis OR Children aged less than 18 years with LDL-C above the 95th percentile for age and sex	2
Clinical history	
Premature coronary artery disease (men <55 years, females <60 years)	2
Premature cerebral or peripheral vascular disease (men <55 years, females <60 years)	1
Physical examination	
Tendinous xanthomata	6
Arcus cornealis prior to age 45 years	4
LDL-C (mmol/L) – 8.5 or higher – 6.5 to 8.4 – 5.0 to 6.4 – 4.0 to 4.9	 8 5 3 1
DNA analysis: functional mutation in the *LDLR*, *APOB* or *PCSK9* gene	8

Stratification of familial hypercholesterolaemia, as determined by total score using the Dutch Lipid Clinic Network Criteria:

- **Definite FH = total score greater than 8**
- **Probable FH = total score between 6 and 8**
- **Possible FH = total score between 3 and 5**
- **Unlikely FH = total score of less than 3**

Identifying index cases and genetic testing

Index cases of FH should be sought among adults with premature cardiovascular disease in different clinical settings (see the flowchart on page 17). In adults, a simple clinical tool based on the Dutch Lipid Clinic Network Criteria should be used to make the diagnosis (Table 1). All patients considered to have FH should be referred to a lipid disorders clinic for further assessment and institution of cascade screening.

Genetic testing for FH must be carried out by an accredited laboratory; diagnostic services are provided by the Department of Molecular and Clinical Genetics at the Royal Prince Alfred Hospital in Sydney, NSW, and the Department of Cardiovascular Genetics at the Royal Perth Hospital in Perth, WA. Genetic testing for FH does not, at present, have a Medicare item number; it can be funded privately or by special arrangement with state health services.

Genetic testing should be offered to all 'index cases' who have a phenotypic diagnosis of FH. When the phenotypic diagnosis of FH is unlikely, genetic testing of the 'index case' need not be carried out. If the genetic testing protocol does not detect a mutation, the laboratory report should include a caveat that the result does not exclude FH due to undetected mutations or mutations in untested genes, particularly if the clinical phenotype is strongly suggestive of FH.

Identifying index cases is central to risk notification and cascade screening, as described in further detail below.

Clinical assessment and management allocation

Adults

Secondary causes of hypercholesterolaemia (e.g. hypothyroidism, nephrosis, corticosteroid therapy) should first be excluded. The diagnosis of FH should be made using both phenotypic and genetic testing. Not all patients with FH have the same risk of CHD; variability depends on genetic and coexistent environmental and acquired factors. Hence, patients should be risk stratified according to the presence of cardiovascular risk factors and a personal history of

cardiovascular disease (see the flowchart on page 18).

Risk stratification should guide the intensity of medical management. It should include assessment of traditional cardiovascular risk factors, as well as prematurity of the family history of CHD and plasma lipoprotein(a) concentration. When practicable and indicated, there should be an assessment of atherosclerosis load, using carotid ultrasonography with particular attention to detection of plaques.

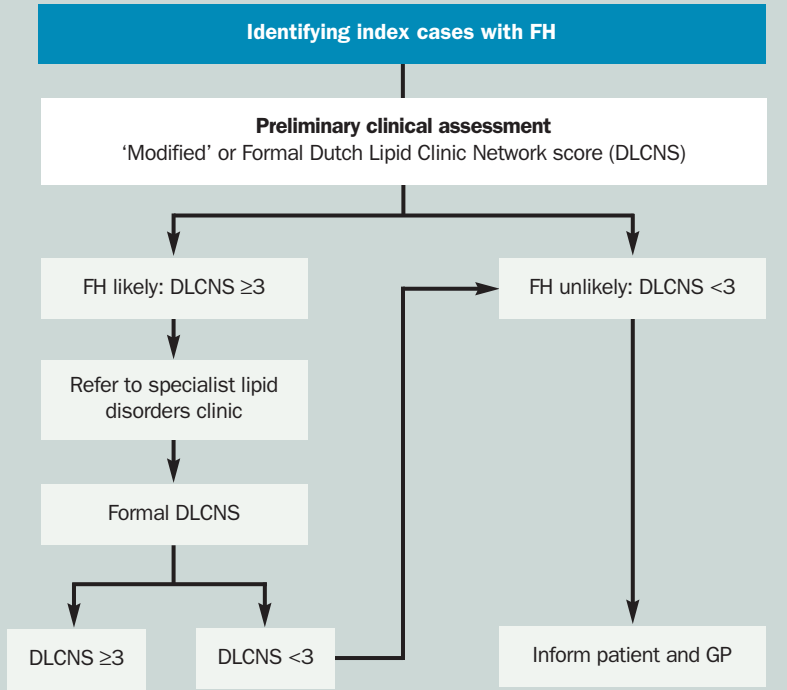
The young

Children (aged 5 years and older) and adolescents should be tested for FH after a diagnosis of FH has been made in a parent. Again, secondary causes of hypercholesterolaemia should first be excluded. With rare exceptions, children and adolescents should only be genetically tested for FH after a mutation has been identified in a parent or first-degree relative.

Age- and gender-specific plasma LDL-C concentration thresholds should be used to make the phenotypic diagnosis, with an LDL-C of greater than 5.0 mmol/L indicating highly probable or definite FH; two fasting lipid profiles are recommended.

Patients should be risk stratified according to age, presence of other cardiovascular risk factors, prematurity of family history of CHD and the level of hypercholesterolaemia at diagnosis. Risk stratification should be used to guide medical management.

Detection of index cases and diagnosis of familial hypercholesterolaemia (FH)



Potential sources for identifying index cases with FH include coronary care, cardiac rehabilitation, cardiothoracic surgery, stroke unit and vascular surgery, ward nursing staff, specialists, GPs, laboratory report alerts, pharmacists, clinical genetics services. It can also be identified opportunistically in clinics/hospitals.

There should be a high index of suspicion for new cases and retrospective auditing of previous cases. Use the simplified modification of phenotypic criteria for FH.

Management

Adults

All patients with FH must receive lifestyle advice and nonlipid cardiovascular risk factors must be corrected. With the very high plasma cholesterol levels seen in patients with FH, it is unrealistic to aim to treat all patients to an LDL-C target of less than 2.5 mmol/L.

Consistent with recognised variations in CHD risk, plasma LDL-C targets for routine, enhanced and intensive management should be less than 4 mmol/L, less than 3 mmol/L and less than 2 mmol/L, respectively. This requires treatment with a fat-modified diet, plant sterols and a statin either with or without ezetimibe. Nicotinic acid, resins and a fibrate may be required with more intensive strategies.

Plasma levels of hepatic aminotransferases, creatine kinase and creatinine should be measured before starting pharmacotherapy. All patients on pharmacotherapy, particularly statins, should have hepatic aminotransferases monitored as required in the product information; an alternative, less cautious option is to monitor hepatic aminotransferase levels only if they are initially elevated. Creatine kinase should only be measured when musculoskeletal symptoms are reported and creatinine should be monitored in those with kidney disease.

Women with FH who are of childbearing age should have prepregnancy counselling. This may involve more detailed assessment of cardiovascular risk, including a stress test for subclinical CHD in at-risk individuals. Statins and other systemically absorbed lipid-regulating agents should be discontinued three months before conception and during pregnancy and breastfeeding.[9]

Noninvasive testing for CHD and atherosclerosis should be considered in patients undergoing standard and enhanced treatment, with a step-up in treatment considered if there is evidence of progression of disease.

Patients receiving standard or enhanced management should be reviewed every six to 12 months; those receiving intensive management should be reviewed according to clinical context, with appropriate interval assessment of cardiac function and referral to a cardiologist.

The young

All children or adolescents with FH should receive advice on lifestyle modifications and nonlipid cardiovascular risk factors must be addressed. Not all young people with FH have the same long-term risk of CHD. Risk stratifying patients allows for a more rational approach to treatment.

Lowest risk patients should be treated expectantly with a fat-modified diet with or without plant sterols. Statin therapy can be considered after the age of 10 years in boys and one year after the menarche in girls.

Plasma LDL-C targets for intermediate- and high-risk patients should be less than 4 mmol/L and less than 3 mmol/L, respectively. A statin with or without ezetimibe may be required.

In Australia, pravastatin, fluvastatin and simvastatin are licensed for use in children, but other statins may be prescribed according to clinical indications, such as in higher risk patients who require more potent statins to reach LDL-C target levels.

Body weight, growth, physical and sexual development, and wellbeing should be reviewed regularly in all children and adolescents with FH. Plasma levels of hepatic aminotransferases, creatine kinase and creatinine should be measured as noted for adults. Carotid artery ultrasonography should be considered for assessing intima-medial thickness and the presence and progression of plaques; this may guide the intensity of medical management, but care should be taken in its application. Consideration should be given to managing children and adults with FH from the same family in a family-centred clinic.

LDL-apheresis: radical therapy

LDL-apheresis should be considered in patients with homozygous or compound heterozygous FH, as well as in those with heterozygous FH and documented CHD who are refractory to, or cannot tolerate, cholesterol-lowering medication. LDL-apheresis may be used in children who present with homozygous or compound heterozygous FH by the age of 5 years, particularly if their plasma cholesterol concentration remains at 9 mmol/L or above on medication.[10]

LDL-apheresis should be carried out in close collaboration with a centre that is experienced in apheresis, such as a transfusion medicine service. Treatment effects on progression of atherosclerosis should be monitored with echocardiography (aortic valve and root), carotid ultrasonography and/or exercise stress testing. LDL-apheresis services in Australia are at present provided by the Austin Hospital in Melbourne, Vic, and the Royal Perth Hospital in Perth, WA.

Cascade screening: risk notification and family testing

Cascade screening is the engine for detecting new cases of FH (see the flowchart on page 20). Notification of relatives at risk of FH should generally not occur without the consent of the index case.

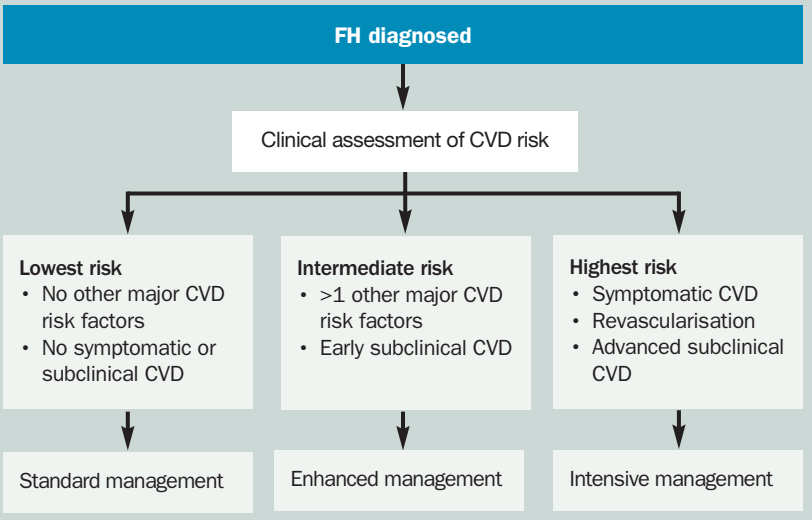
If no consent is given by the index case, rapport should be built and consideration given to referring the patient for genetic or other types of counselling. Relatives should only be directly notified of their risk without consent of the index case if there is specific legislative provision for this breach of confidentiality in the relevant jurisdiction. Federal Government legislation, local state legislation, NHMRC guidelines and local health service protocols about disclosure of medical information without consent should be consulted.

A proactive approach that respects privacy and autonomy is required. All material sent to relatives and any contact with them should be comprehensible and not cause alarm. General and specific modes of communication should be used.

Cascade screening should ideally be carried out as a formal collaborative process between lipid disorders clinics and clinical genetics services. It should also involve close communication and liaison with primary care physicians and employ a user-friendly, family-based data management system. Pretesting counselling should be offered to at-risk family members of an index case before phenotypic or genetic testing is performed. If no consent or assent for genetic testing is obtained then phenotypic testing for FH should be offered.

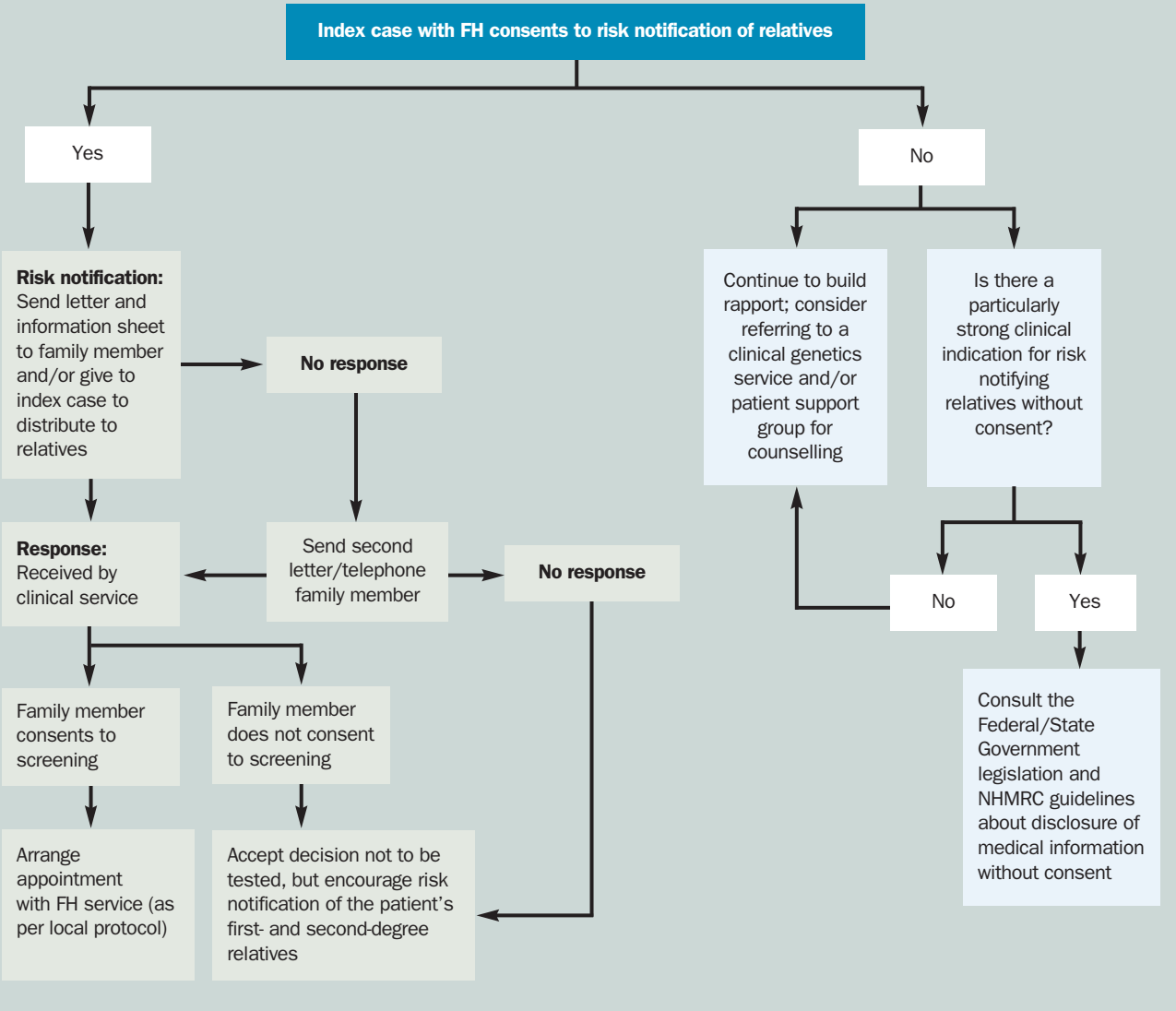
If genetic testing detects the family mutation, a definitive diagnosis of FH can be made in the tested individual, particularly when the phenotype also suggests FH. If genetic testing does not detect the family mutation, the diagnosis of FH can be excluded, except when the clinical phenotype is highly suggestive of FH.

Assessment of adult patients with familial hypercholesterolaemia (FH)



ABBREVIATION: CVD = cardiovascular disease.

Cascade screening for familial hypercholesterolaemia (FH): risk notification and how to approach families



Conclusion

The recommendations of this model of care are generally congruent with other recently published guidelines for FH.[11-14] However, in contrast to recent US guidelines, we do not recommend universal screening for hypercholesterolaemia in children aged 9 to 11 years because the practicability and cost-effectiveness of this approach are unclear.[12] The reader is referred to our main publication for more details and discussion of the recommendations, as well as additional clinical care pathways and protocols.[8]

The model of care builds on the work of previous guidelines by providing specific recommendations concerning integration of services, administrative and information technology requirements, clinical governance, teaching and credentialing, and establishing a family support group.[8] However, our model of care is centred on lipid disorders clinics in tertiary centres, and the full integration of this model into primary care needs to be developed and tested. Effectively implementing and sustaining the uptake of these recommendations in routine clinical practice, with appropriate funding mechanisms, remains the biggest challenge for the future. **CT**

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A list of references is available on request to the editorial office.

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