COMMENTARY

Familial hypercholesterolaemia: a review with emphasis on evidence for treatment, new models of care and health economic evaluations

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Abstract

Familial hypercholesterolaemia (FH) is a condition that should be familiar to all health professionals involved in preventive medicine. FH is the most common and serious monogenic disorder of lipid metabolism that leads to premature coronary heart disease. However, most cases remain undetected or inadequately treated in our community. We provide an overview of FH, with emphasis on evidence for treatment, new models of care (MoCs) and health economic evaluations. Evidence for treatment is based on cohort studies; while this is a low level class of evidence, MoCs concur in recommending early intervention and lowering of plasma low-density lipoprotein-cholesterol levels by at least 40% with statins. Preliminary health economic evaluations suggest that detecting and treating FH is cost-effective, but further studies based on high-quality international data and standardised costing methods are needed. If the recommendations in the published MoCs are followed, there is likely to be significant improvement in the health and quality of life of patients with FH and their families, as well as major cost savings in healthcare for end-organ damage, including myocardial infarction, acute coronary syndromes and possibly stroke, but this requires to be verified.

Key words: detection, evidence, familial hypercholesterolaemia, health economic evaluation, model of care, treatment.

Introduction

Familial hypercholesterolaemia (FH) is the most common and serious monogenic disorder of lipid metabolism (OMIM number: #143890) that leads to premature coronary heart disease (CHD). The prevalence of FH is estimated to be at least one in 500 in the population, but in spite of major advances in scientific and clinical knowledge about the condition, most cases remain undetected or inadequately treated in our community. To meet this demand, models of care (MoCs) for FH have recently been published, but their cost-effectiveness has not been fully evaluated. We provide a brief review of FH, with an emphasis on evidence for treatment, new MoCs, and health economic evaluations (HEEs). Gaps in evidence and suggestions for further investigation are identified.

Pathophysiology

Cholesterol is a lipid that constitutes a structural component of cell membranes and is the precursor of steroid hormones, vitamin D and bile acids. Cholesterol is chiefly carried in the circulation packaged in low-density lipoprotein (LDL) particles which are formed from very-low-density lipoprotein secreted by the liver. Circulating LDL-cholesterol is predominantly cleared via the liver by a tightly regulated LDL receptor pathway that involves particle binding and internalisation, endosome formation, cholesterol release to the cell and recycling of the receptor back to the cell surface. In FH, there is a defect in the LDL receptor pathway that leads to decreased clearance of LDL-cholesterol from plasma.

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with a consequent increase in the concentration of total and LDL-cholesterol. The defect is genetic and can occur at several levels: LDL receptor synthesis, transport to cell surface, internalisation and release from endosomes. Genetic defects in apolipoprotein B-100 (apoB), the ligand for the receptor, and in proprotein convertase subtilisin/kexin type 9 (PCSK-9), an enzyme that degrades the receptor, similarly impair the catabolism of LDL-cholesterol and elevate the plasma concentration of LDL-cholesterol. The degree of elevation in plasma cholesterol in FH is hence dependent on the extent of the defect in LDL catabolism which is in turn dependent on the severity of the genetic mutation.

**Molecular pathology**

Familial hypercholesterolaemia is an autosomal co-dominantly inherited disorder caused primarily by mutations in the gene that encodes the LDL receptor on the short arm of chromosome 19. The inheritance of FH is autosomal dominant, with a high degree of phenotypic penetrance. Hence, parents with heterozygous FH have a 50% chance of passing on the affected gene to each offspring. Figure 1 shows a typical pedigree depicting the dominantly inherited phenotype in a family with heterozygous FH. More than 1000 mutations in the LDL receptor have been reported and their detection forms the basis for making a definitive diagnosis of the condition. In heterozygous FH, only 50% of the LDL receptors are functional and this typically increases plasma LDL-cholesterol concentration from 5 to 12 mmol/L. In homozygous and compound heterozygous FH, all LDL receptors are absent or dysfunctional, and, consequently, LDL-cholesterol concentration increases to >12 mmol/L. Autosomal recessive hypercholesterolaemia (ARH) is extremely rare and its molecular basis remains unknown. Other causes of autosomal-dominant hypercholesterolaemia are familial ligand-defective apoB-100 (FDB) due to mutations in the apoB gene and rare mutations in the PCSK-9 gene (also known as FH3). Despite normal LDL receptors, these mutations have the same functional consequences on the clearance of LDL-cholesterol from plasma as classical LDL receptor mutations; they collectively account for less than 6% of cases presenting with phenotypic FH.

**Cardiovascular pathology**

Marked elevation in the plasma concentration of LDL-cholesterol in FH leads to endothelial dysfunction and uptake of LDL-cholesterol by the arterial wall, thereby accelerating atherogenesis and cholesterol-laden foam cell formation in affected individuals from birth. The rate of development of atherosclerosis is on average directly proportional to the LDL-cholesterol concentration, and is hence much higher in homozygous than heterozygous patients. Atherosclerosis leads to severe left main or triple vessel coronary disease, but can also affect the root of the aorta and extend to the aortic valve cusps, especially in homozygotes. Atherosclerotic involvement of the femoral and cerebral arteries is much less common and reflects the predilection of LDL-cholesterol to injure the proximal coronary arteries.

**Epidemiology and natural history**

Heterozygous FH is commonly considered to affect one in 500 people in most populations, but its actual prevalence

![Figure 1](https://example.com/figure1.png)

**Figure 1** Hypothetical pedigree tree depicting dominantly inherited phenotype in FH.
may be considerably higher. The prevalence of FH is higher in first-degree relatives (one in two) of index cases than in the general population. The prevalence is also higher in populations subject to a ‘founder gene effect’, such as the Afrikaners (1:70), Lithuanian Jews (1:70), Christian Lebanese (1:170) and Québécois (1:200). Patients with heterozygous FH occur as commonly in our community as those with type 1 diabetes mellitus or HIV infection. The prevalence of compound heterozygous FH (two different mutations) is considered to be one in 250 000 (1/500 × 1/500) and true homozygous FH (same mutation) one in 104 (1/4 × 1/500 × 1/500). Underdiagnosis of FH is a universal problem. There are estimated to be at least 10 million subjects with FH worldwide, and at least 40 000 in Australia. Conservatively, we estimate that, in Australia, at least 80% of cases of FH remain undetected and almost certainly untreated. This represents a major gap in care, because if untreated, one in two male heterozygous patients and one in six of their female counterparts will develop fatal CHD by age 60. Since the introduction of statins, life expectancy in heterozygotes has approached that of the background population, but their standardised mortality rate for CHD remains high at 2.5. Subclinical CHD develops from youth, but its clinical manifestation varies widely among affected individuals, variation being less among those from the same pedigree, in whom the clinical phenotype is dependent on inheritance of the family mutation. Homozygotes and individuals inheriting different defective LDL receptor genes from both parents (i.e. compound heterozygotes) can develop aggressive CHD in childhood, and without radical medical therapy and cardiac surgery or liver transplantation will usually sustain a fatal myocardial infarction before the age of 30.

**Signs and symptoms**

The deposition of cholesterol in tissue macrophages in tendon sheaths results in xanthomas. These are typically present in the Achilles and extensor tendons of the hands in more than 70% of patients with FH by age 45. Inflammation of the tendons not infrequently presents as Achilles tenosynovitis. Homozygotes have striking skin and tendon xanthomas by age 10. Tendonopathies are pathognomonic of FH, but they may also be seen very rarely in type III hyperlipidaemia and beta-sitosterolaemia. Arcus cornealis before the age 45 is another diagnostic feature of FH, but above this age is a non-specific physical sign. Absence of xanthomas or arcus cornealis does not exclude FH, and this is particularly pertinent in younger patients. Patients with heterozygous FH can develop symptomatic CHD in their 30s and 40s, particularly if they are untreated and have other risk factors (smoking, hypertension, diabetes) and a strong family history of CHD. Homozygous patients can present with symptomatic CHD in childhood and adolescence. An aortic systolic murmur is highly indicative of supravalvular aortic stenosis, which is much more common in homozygotes than heterozygotes.

**Diagnosis: value and limitations of genetic testing**

The diagnosis of FH is based on clinical, biochemical and genetic criteria. The two commonly employed diagnostic tools are the Simon Broome and Dutch Lipid Clinic Network (DLCN) criteria that assign a probability rating for having FH based on the personal and family history of premature CHD and hypercholesterolaemia, clinical stigmata of FH and the presence of a pathogenic mutation. Both these diagnostic tools are equally useful clinically, noting that the detection of arcus cornealis is not required by the Simon Broome criteria. The DLCN criteria are internationally most popular and are shown in Table 1. Hypercholesterolaemia cannot be used as a criterion with either tool if plasma triglycerides exceed 4.5 mmol/L, in which case other conditions such as type III hyperlipidaemia should be considered. When screening relatives, it may be preferable to use age- and gender-related thresholds for plasma LDL-cholesterol concentrations, for in such individuals with a one in two chance of having FH, the fixed cholesterol levels in the Simon Broome tool may not be sufficiently sensitive.

<table>
<thead>
<tr>
<th>Family history</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>First degree relative with known LDL-cholesterol above the 95th percentile for age and sex</td>
<td>2</td>
</tr>
<tr>
<td>First degree relative with tendon xanthoma and/or arcus cornealis</td>
<td>2</td>
</tr>
<tr>
<td>Clinical history</td>
<td>Score</td>
</tr>
<tr>
<td>Patient with premature coronary artery disease (ages as above)</td>
<td>2</td>
</tr>
<tr>
<td>Patient with premature cerebral or peripheral vascular disease (as above)</td>
<td>1</td>
</tr>
<tr>
<td>Physical examination</td>
<td>Score</td>
</tr>
<tr>
<td>Tendonous xanthoma</td>
<td>6</td>
</tr>
<tr>
<td>Arcus cornealis prior to age 45 years</td>
<td>4</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/L)</td>
<td>Score</td>
</tr>
<tr>
<td>LDL-C ≥8.5</td>
<td>8</td>
</tr>
<tr>
<td>LDL-C 6.5–8.4</td>
<td>5</td>
</tr>
<tr>
<td>LDL-C 5.0–6.4</td>
<td>3</td>
</tr>
<tr>
<td>LDL-C 4.0–4.9</td>
<td>1</td>
</tr>
<tr>
<td>DNA analysis – functional mutation in the LDLR, APOB or PCSK9 gene</td>
<td>8</td>
</tr>
</tbody>
</table>

**Stratification**

<table>
<thead>
<tr>
<th>Total score</th>
</tr>
</thead>
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<tr>
<td>Definite FH</td>
</tr>
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<td>Probable FH</td>
</tr>
<tr>
<td>Possible FH</td>
</tr>
<tr>
<td>Unlikely FH</td>
</tr>
</tbody>
</table>
However, because of overlap with other causes of moderately elevated cholesterol, deficiencies in obtaining accurate family histories and the subtleties of physical signs, the best way of making a definitive diagnosis of FH is by genetic testing for a causative mutation.\textsuperscript{21} Plasma cholesterol values in children are lower than adults and this can present diagnostic ambiguity when screening families for children potentially affected by heterozygous FH.\textsuperscript{8,22} While recently published diagnostic levels for LDL-cholesterol may be useful,\textsuperscript{21} genetic testing is the best approach in children once the causative mutation is known in the affected parent.\textsuperscript{8,22} The molecular diagnosis of FH is at present labour-intensive and expensive. This is because of the present need for extensive exon-by-exon sequence analysis (EBESA) of the LDL receptor gene, in the absence of validated DNA technologies (in development) to a level acceptable for routine diagnostic laboratories.\textsuperscript{21} Structural rearrangements in the LDL receptor gene, including large deletions and duplications, cannot be detected by conventional DNA (EBESA) analytical methods.\textsuperscript{21} Additionally, the extensive genetic heterogeneity of FH means that beyond the LDL receptor gene, genetic variants in FDB, PCSK-9 and ARH have to also be considered.\textsuperscript{1,10,21} A rational approach to genetic testing using a combination of commercial methods and EBESA in people who are likely to have FH on clinical grounds has been proposed,\textsuperscript{8} but its cost-effectiveness remains to be evaluated. Even with this method, mutations may not be detected in up to 30% of patients with definite phenotypic FH. Genetic testing for FH should only be carried out by an accredited centre,\textsuperscript{8} and in Australia is at present only offered by two NATA-accredited laboratories in Perth and Sydney. While the value of genetic testing is accepted by practitioners and consumers,\textsuperscript{21,24} key questions that need to be addressed are whether it offers greater prediction of risk of CHD than the plasma level of LDL-cholesterol and whether it can usefully predict the response to statin therapy.\textsuperscript{21} Issues related to lay understanding, health literacy,\textsuperscript{25} psychological sequelae\textsuperscript{26} and perceived risks\textsuperscript{26,27} concerning the use of genetic testing in routine practice require further investigation. The use of genetic testing for FH in primary care also needs to be developed and tested,\textsuperscript{28} as does the role of nurses in genetic counselling.\textsuperscript{29}

**Clinical assessment**

Patients should have a detailed clinical assessment to investigate other cardiovascular risk factors (obesity, diabetes, hypertension, smoking), presence of symptomatic or subclinical atherosclerosis (e.g. carotid ultrasonography) and secondary causes of hypercholesterolaemia (hypothyroidism, nephrotic syndrome, corticosteroids).\textsuperscript{8,18,20} The importance of assessing other cardiovascular risk factors beyond hypercholesterolaemia is underscored by the rising incidence of obesity, type 2 diabetes and hypertension in our community.\textsuperscript{30} Clinical assessment must take account of the psychological, intellectual, literacy, social and cultural status of the patient.\textsuperscript{8} FH patients may be pragmatically categorised into lowest, intermediate and highest risk of cardiovascular disease (CVD): lowest risk indicating no other cardiovascular risk factors and negative tests for subclinical atherosclerosis; intermediate risk indicating at least one other cardiovascular risk factor or subclinical evidence of atherosclerosis (plaques); highest risk indicating a history of symptomatic CVD (coronary, cerebral or peripheral vascular disease) and/or a revascularisation procedure.\textsuperscript{8} Heterozygous children aged less than 10 years may be considered to have low-risk FH and those older than 10 years may be considered to have higher-risk FH, particularly with a family history of very premature CVD, two or more major cardiovascular risk factors, or LDL-cholesterol >6.0 mmol/L.\textsuperscript{8,9,22} To the extent that severe pathogenic mutations (e.g. large truncations, compound heterozygosity) predict the degree of elevation in plasma LDL-cholesterol, genetic testing may also be employed in risk stratification. Whether genetic testing may also be useful in assessing the pharmacodynamic response to or the side-effects of cholesterol lowering therapy remains to be established. Stratification of risk in FH allows tailoring of management and best use of resources, but the cost-effectiveness of this strategy also requires further evaluation. Patients considered to have a homozygous FH phenotype are at exceptionally high risk and should be considered for LDL-apheresis.\textsuperscript{8,31}

**Treatment: targets, options and evidence**

In parallel with lowering elevated plasma cholesterol concentrations, appropriate lifestyle modifications should be emphasised and all major non-lipid cardiovascular risk factors must be treated according to expert guidelines.\textsuperscript{8} Diets should be low in saturated fat and energy and adjusted to achieve desirable body weight. Dietary supplementation with plant sterols (or stanols) should be considered, but, in children, increased intake of fruit and vegetables should be required to prevent reduction in plasma carotenoid levels owing to decreased absorption mediated by plant sterols.\textsuperscript{8,20} In spite of the value of healthy diets, almost all patients with FH will require medication to lower elevation in plasma LDL-cholesterol.

**Treatment targets: LDL-cholesterol and apoB targets**

The recommended primary therapeutic targets for the absolute plasma concentration of LDL-cholesterol are <4.0, <3.0 and <2.0 mmol/L for adult FH patients with lowest, intermediate and highest risk of CVD, respectively.\textsuperscript{8,20} These targets are compatible with other therapeutic guidelines for the management of hypercholesterolaemia.\textsuperscript{20,32–34} Therapeutic targets should evidently be lower with increasing CVD risk. In patients with plasma triglyceride levels >2.0 mmol/L (typically with coexisting diabetes or metabolic syndrome), an apoB target of <0.8 g/L is reasonable after the LDL-cholesterol target is achieved.\textsuperscript{8,20,35} With other guidelines recommending for no good reason use of non-high-density lipoprotein (HDL) cholesterol targets,\textsuperscript{35} there are no targets for plasma HDL-cholesterol concentration. Even with contemporary treatments, achieving the absolute targets for
LDL-cholesterol may not be attainable by some patients, particularly those with higher baseline plasma cholesterol, in which case, a more realistic general target of a 40 to 50% reduction from pretreatment levels could be used.\textsuperscript{6,9} The use of the foregoing therapeutic targets is supported by clinical trials in non-FH populations at high risk of CVD,\textsuperscript{36–38} as well as surrogate endpoint trials in FH subjects.\textsuperscript{39–42} However, the value of treating FH patients to these targets has not been specifically tested in clinical endpoint trials.\textsuperscript{4,43} In children and adolescents, there is also no hard evidence on which to base therapeutic targets, but an LDL-cholesterol reduction of 40% is a reasonable and agreed recommendation.\textsuperscript{5,22,41}

**Pharmacotherapy: level of evidence**

HMG CoA reductase inhibitors (or statins) are by far the most effective drugs to treat hypercholesterolaemia in FH. Several large-scale, placebo-controlled trials support the effectiveness and safety of statins in decreasing cardiovascular events in a wide spectrum of individuals, some of whom had hypercholesterolaemia, in both primary and secondary prevention settings.\textsuperscript{36–38} All statin clinical trials have used a fixed dose of the drug, with no specific evidence available for dose adjustment, and benefit has been reported to be independent of pretreatment plasma concentration of LDL-cholesterol and the response of LDL-cholesterol to statins.\textsuperscript{36–38} These placebo-controlled trials have not, however, included patients with FH, because it is unethical to withhold treatment from patients with severe hypercholesterolaemia at very high lifetime risk of CHD.\textsuperscript{42} Randomised clinical trials employing surrogate end-points, such as endothelial function, carotid intima-media thickness and angiographically defined coronary atherosclerosis,\textsuperscript{39,41} support the use of statins and cholesterol-lowering agents in decreasing cardiovascular events in patients with FH. Two observational studies from Europe provide evidence that long-term statin therapy decreases CHD events and mortality in FH to a level comparable to that of the background population.\textsuperscript{16,17} The level of evidence supporting the use of statins in FH is therefore based on relatively small cohort studies alone and small surrogate endpoint trials. Given the serious nature of FH if left untreated, this level of evidence does not diminish the strength of expert recommendations to start statins early and lower LDL-cholesterol to targets in this condition.\textsuperscript{6–9}

Hence, there are reasonably good longitudinal data suggesting that statins decrease the incidence of CHD in FH.\textsuperscript{16,17} Statins are also estimated to be cost-effective in treating FH.\textsuperscript{43,44} Reduction in the costs of statins will, however, make the medical care for FH even more cost-effective in the future. After initiation of statin therapy, all patients should be reviewed at 6 to 8 weeks to monitor LDL-cholesterol response, adherence, safety parameters and tolerability, and 6 to 12 months thereafter if targets are achieved and no problems are documented.\textsuperscript{8} The statin should be up-titrated to the maximally recommended tolerable dose that achieves therapeutic targets; patients may require switching to more potent statins, such as atorvastatin or rosuvastatin.

Despite the lack of outcome evidence, the value and safety of prescribing statins for children and adolescents with FH is universally recognised.\textsuperscript{6–8,45–47} As a general guide, boys older than 10 years and girls who have reached menarche should be considered for statin therapy.\textsuperscript{6,8} The specific age at which to introduce a statin is not evidence-based and in practice should be determined by good clinical judgment and assessment of several factors, including family history of premature CVD, the prevailing plasma level of LDL-cholesterol, the type of FH mutation identified and the presence of other cardiovascular risk factors (e.g. diabetes mellitus).\textsuperscript{8} All children and adolescents on statins require monitoring of physical growth and pubertal development, as well as, when indicated, plasma levels of hepatic aminotransferases, creatine kinase and creatinine.\textsuperscript{8,48} Statins are contraindicated in pregnancy and during lactation.\textsuperscript{49} More systematically collected long-term safety data are required on the use of statins and other lipid-regulating agents in paediatric FH. Adherence and persistence with therapy is a common problem,\textsuperscript{50} and in adolescents with FH may need special monitoring and counselling.\textsuperscript{51}

Higher-risk FH patients who require greater lowering of plasma LDL-cholesterol and apoB will require other drugs, especially ezetimibe, but also niacin, fenofibrate and bile-acid binding resins.\textsuperscript{5,20} Combination drug regimens that target LDL-cholesterol can decrease progression of CHD in patients with FH.\textsuperscript{41} Clinical trials in higher-risk, non-FH subjects support the use of non-statin lipid-regulating drugs in decreasing CHD events.\textsuperscript{52,53} With fibrates, the evidence is strongest in diabetic patients with atherogenic dyslipidaemia, characterised by plasma triglycerides >2.2 mmol/L and HDL-cholesterol <1.0 mmol/L.\textsuperscript{53,54} This is important because up to one-third of FH patients may have metabolic syndrome.\textsuperscript{8,18,55} The value of niacin as an add-on to statins in this context has recently been questioned by results from an intermediate size trial.\textsuperscript{56} Niacin may, however, be particularly indicated for lowering high plasma Lp(a) and LDL-cholesterol concentrations in FH rather than regulating elevated triglycerides and low HDL-cholesterol in those at and near to LDL-cholesterol targets.\textsuperscript{52,53,57} Hence, residual hypertriglyceridaemia and low HDL-cholesterol in an FH patient on a statin is an indication for considering treatment with fenofibrate, niacin or higher doses of supplemental omega-3 fatty acid ethyl esters,\textsuperscript{20,52–54} noting that there is no outcome evidence in this specific group to support this recommendation.

**Models of care for FH: translational and transfer requirements**

Several guidelines have been published on how to diagnose and manage FH.\textsuperscript{6–9,22,33} The general approach has been to identify key clinical questions and provide guidance for practitioners based on a systematic review of the literature and evidence based chiefly on expert opinion. The clinical recommendations made were based on priorities that were likely to have the highest impact on patient outcomes and lead to more efficient use of resources. The most comprehensive clinical guideline that provides a classical
overarching MoC for FH has been provided recently by the FH Australasia Network. The basic elements considered by the Australasian model are shown in Figure 2. The recommendations for detecting and managing FH in the present article are based on this model.

With some notable differences, FH guidelines are generally congruent in their recommendations on methods of case detection and cascade screening, approach to children and adolescents, lifestyle and drug treatment strategies and indications for LDL-apheresis. By contrast to Europe and Australia, the National Lipid Association in the US recommends universal screening for hypercholesterolaemia (particularly among 9- to 11-year-olds), other international recommendations specifying targeted screening of potential index cases in coronary care units and primary care, followed by a vigorous but ethically regulated family tracing strategy. The choice of clinical tools for diagnosing adult FH is from the Make Early Diagnosis – Prevent Early Death, Simon Broome and DLCN criteria. The latter is probably the most sensitive and is preferred in continental Europe and Australasia.

European and Australian approaches also stress the value of genetic testing of FH within families following the detection of a pathogenic mutation in an index case, but all agree that a combined phenotypic and genetic testing strategy offers the most effective approach for detecting new cases. An efficient laboratory protocol based on serially testing for genetic variants individuals with at least a possible phenotypic diagnosis of FH by commercial methods, multiplex-igation probe amplification (for large deletions) and exon-by-exon sequencing has been described, but may be superseded with the advent of more sophisticated chip-microarray methods and next-generation sequencing.

The Australasian guidelines uniquely underscore the value of non-invasive imaging of atherosclerosis in assessing and managing FH patients without clinically demonstrable coronary disease, but stress the importance of employing a fully credentialled vascular imaging service and estimating carotid arterial wall dimensions with edge-detection software. A universally agreed target treatment level for heterozygous patients is at least a 40% reduction in plasma LDL-cholesterol concentration, the Australasian MoC specifying target of <4.0, <3.0 and <2.0 mmol/L for patients with lowest, intermediate and highest risk, respectively. Figure 3 shows the risk stratification strategy recommended by the Australasian guidance for people diagnosed with FH and the rationalisation of management into standard (review interval every 12 months), enhanced (review every 6 months) and intensive (review interval <6 months and as required). Lifestyle changes are underscored by all

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Figure 2 Basic elements of the Australasian model of care for FH.

Figure 3 Risk stratification of patients diagnosed with FH with management allocation and treatment targets for plasma LDL-cholesterol.
guidelines. Statins, with or without other agents, are required to meet these targets and careful pretreatment checks on liver and muscle enzymes are required, with regular monitoring of plasma aminotransferases and (if myalgia is reported) checking of creatine kinase. The safety of statins in children is reaffirmed and their use over the age of 10 years is advised. Uniform recommendations are given for avoiding statins in women during (or planning) pregnancy and lactation, and choosing low oestrogen or progesterone-only oral contraceptives, with barrier methods preferred, in women with FH.

The Australasian MoC aims to establish a standard of care for FH patients in a framework within which future evidence and consensus may be included and developed. It extends other proposed clinical care programs from Europe and the US, providing lucid clinical care algorithms and recommendations concerning integration of services, administrative and information technology requirements, clinical governance, teaching and credentialing and establishing a family support group. The MoC is intended primarily for lipid disorder clinics in tertiary centres intending to initiate or develop a clinical service for FH. Further MoCs for general practice and the role of nursing practice need to be more fully defined. Publishing guidance and a MoC for FH is a one thing, but effectively implementing and ensuring uptake of recommendations is another, a challenge well emphasised by recent reports from several countries. Implementation and effective sustainability are where the real challenges lie.

This requires close collaboration between clinical, bureaucratic and political stakeholders to translate the evidence into government healthcare policy. Financial support may come directly from government or from alternative private–public revenue sources. Since policy-making draws on the values and priorities of the population, it is essential to raise community awareness about the beliefs of early detection and treatment of FH. We emphasise that MoCs for FH need to be effectively translated and transferred into clinical care within the framework of the Chronic Care Model, but, as importantly, they need to be subjected to regular auditing and HEE. This will allow service models to grow into a standard of excellence for the care of all patients with FH.

**HEEs: evidence gap?**

The success and sustainability of systematic screening and early treatment of patients with FH relies on adequate funding for these programs. To make a case for government funding of FH programs requires a detailed and robust HEE of the detection of index cases, cascade screening of families and treatment of patients identified as having FH. HEEs for FH programs (but not formal MoCs) and alternative recruitment strategies have been presented from Spain, the Netherlands and the UK. In general, cascade screening and treatment with statins appear to be cost-effective. The cost to detect one new case of FH has been reported to range from AUD1237 (lipid profile) and AUD1829 (DNA test) to AUD955 (lipid profile plus DNA test). This needs further evaluation in respect of DNA testing based on comprehensive genetic analysis, commercial methods and chip-microarrays. Table 2 summarises the cost-effectiveness of cascade screening for FH, including treatment, as cost per life year gained and cost per quality-adjusted life year. Cost per life year gained has been estimated to range from AUD1829 (DNA test) to AUD955 (lipid profile plus DNA test). These HEEs have not been carried out using uniform methods and have been limited by poor availability of robust outcome data in FH. To date, outcome data relating to the full range of cardiovascular morbidity, including myocardial infarction, unstable angina, revascularisations, stroke and peripheral arterial disease are not widely available in the literature and have not been employed in assessing cost-effectiveness. Furthermore, some HEEs have been based on data derived from statin trials that have not specifically included patients with FH, or have estimated treatment benefits from Framingham Risk Equations that are not

### Table 2 Cost-effectiveness of cascade screening and treatment in FH

<table>
<thead>
<tr>
<th>Source</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Base case analysis ICER (AUD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nherera et al. 2011</td>
<td>Cascade screening using cholesterol method</td>
<td>Cascade screening using genetic and cholesterol methods</td>
<td>5 393/QALY‡</td>
</tr>
<tr>
<td>Nherera et al. 2010</td>
<td>Low potency statin</td>
<td>High potency statin</td>
<td>16 539/QALY‡</td>
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<tr>
<td>Oliva et al. 2009</td>
<td>No screening</td>
<td>Genetic cascade screening</td>
<td>3 960/LYG§</td>
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<tr>
<td>Alonso et al. 2008</td>
<td>Lipid lowering therapy based on normal clinical practice</td>
<td>Atorvastatin 40 mg</td>
<td>3 485/LYG§</td>
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<tr>
<td>Wondering et al. 2004</td>
<td>No screening</td>
<td>Genetic cascade screening</td>
<td>10 071/LYG§</td>
</tr>
<tr>
<td>Marks et al. 2003</td>
<td>No screening</td>
<td>Family tracing – first degree relatives of known cases</td>
<td>4 790/Death averted‡</td>
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<tr>
<td>Marang-van de Mheen et al. 2002</td>
<td>No screening</td>
<td>Genetic cascade screening and treatment of untreated FH positives</td>
<td>36 856/LYG§</td>
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<tr>
<td>Marks et al. 2002</td>
<td>No screening</td>
<td>Universal screening of 16yr olds using clinical strategy</td>
<td>4173/LYG§</td>
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<td>Lovastatin 20 mg</td>
<td>Lovastatin 40 mg</td>
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<td></td>
<td></td>
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<td>Women 14 928/LYG</td>
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</tbody>
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1The costs were updated to 2011 using total health price index for individual country, and then were converted to Australian dollars. 2Cost-effectiveness analysis. ICER, incremental cost-effectiveness ratio; LYG, life year gained; QALY, quality-adjusted life years.
designed for FH. The HEEs are clearly sensitive to the contemporary costs of statins, as evidenced by the higher treatment costs in earlier analyses. It is also unclear whether all patients included in the HEEs of FH had a definite diagnosis of the condition or other causes of hypercholesterolaemia, such as polygenic disorders or familial combined hyperlipidaemia. Most importantly, the analyses have not fully evaluated the cost-effectiveness of treating younger compared with older subjects. Other important considerations that have been omitted are the benefits to individuals with FH from treatment of other CHD risk factors, including smoking, obesity and hypertension, nor the full costs of the long-term care of patients in primary care and specialist centres. Furthermore, cost-effectiveness studies have been specific to their reference market, and it may not be valid to extrapolate economic data to other international settings.

Another limitation is that the economic benefits of detecting and treating FH from a societal perspective have not been evaluated, but this is owing to a lack of available data. Given the collective limitations of the aforementioned analyses, we consider that new frameworks need to be established to enable more comprehensive HEEs to be undertaken and thereby provide health policy decision makers and commissioners with the critical evidence for selecting how best to implement MoCs for FH.

**Conclusion**

Familial hypercholesterolaemia is a condition that should be familiar to all health professionals involved in preventive healthcare. Because hypercholesterolaemia is inherited from birth, it is a pervasive and lifelong risk factor for CHD. There is a major shortfall in the detection and treatment of people with FH in our community, with many young and productive individuals succumbing to premature CHD. The costs of inadequate treatment are immense for individuals with FH and their families. MoCs advocate early identification of index cases through opportunistic and targeted screening, followed by cascade testing of close relatives. A simplified algorithm for detecting and managing FH is shown in Figure 4, but this requires evaluation of its cost-effectiveness in practice mode. Genetic testing provides the most reliable test to make a definitive diagnosis of FH. Genetic testing is, however, only adjunctive to a good clinical history and physical examination and measurement of plasma LDL-cholesterol concentration for assessing and managing FH, noting that up to 30% of phenotypic patients may not exhibit a pathogenic mutation. Treatment for FH relies on judicious use of drugs, especially statins, and lifestyle measures. The evidence for treatment is based on cohort studies and, while this is a low level class of evidence, MoCs provide a strong recommendation for early intervention and lowering of plasma LDL-cholesterol levels by at least 40%. Given that placebo-controlled trials cannot be carried out in FH, the evidence for treatment will continue to rely on cohort studies and more extensive outcome data are required from international sources particularly in the young. Preliminary HEEs suggest that detection and treatment of FH is cost-effective. Further HEEs are, however, required based on high-quality international data and standardised costing methods to strengthen the case for investing in programs for managing FH. This information is critical for lobbying, campaigning and convincing governments to fund comprehensive services for FH that are so sorely needed in their communities. We consider that if a fraction of the recommendations in the published MoCs are followed, the returns will be a significant improvement in the health and quality of life of
patients with FH and their families, as well as major cost savings in healthcare for end-organ damage, including myocardial infarction, acute coronary syndromes and, possibly, stroke. This does not, however, negate the value of critical evaluation and continual modification of existing MoCs for FH that need to be adapted and tested for use in primary care and more explicitly define the role of allied health professionals, particularly nurses and genetic counsellors.

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