Familial hypercholesterolaemia remains largely unrecognised and undertreated in Australian primary care. A new approach involving increased awareness, early detection, lifelong treatment and cascade testing of relatives is essential to improve outcomes of patients with this disorder.

**KEY POINTS**

- Familial hypercholesterolaemia (FH) is a relatively common inherited disorder of high cholesterol levels.
- FH can lead to atherosclerosis, premature coronary artery disease and early death if left untreated.
- Cascade testing of relatives of patients with FH is cost-effective and necessary as one in two will have the condition.
- Innovations in primary care can improve FH detection in the community.
- An integrated approach to FH detection involving GPs, specialists and pathology laboratories is recommended.
- Primary care teams are well positioned to provide a sustainable approach to FH diagnosis and management but greater awareness of this condition is needed.

**Familial hypercholesterolaemia** (FH) is a relatively common, autosomal dominant, inherited disorder of lipid metabolism that can cause atherosclerosis, premature coronary artery disease (CAD) and early death if left untreated. The significance of FH is generally not well appreciated among GPs and patients in the Australian community, with the result that most affected individuals remain undiagnosed, while many who are detected are often inadequately treated. The condition is caused by a defect in the LDL-receptor pathway and results in elevated total and low density lipoprotein cholesterol (LDL-c) levels in the bloodstream from birth. The increased lifelong exposure to LDL-c accelerates the atherosclerotic process.

As FH is autosomal dominant, children of affected individuals have a 50% chance of inheriting the condition. For males with FH, the risk of developing CAD before age 50 years is 50%, whereas for females it is 30% before age 60 years. As people with FH are already at very high risk, the use of cardiovascular disease (CVD) risk calculators to assess absolute risk in FH patients is not appropriate. The marked acceleration of coronary atherosclerosis in people with FH means that young patients with FH have much to gain from early diagnosis and treatment. Effective...
and early treatment of FH with statin therapy reduces the lifetime exposure to very high cholesterol levels with the concomitant reduction in CAD events largely offsetting the cost of prolonged treatment.\(^5\) It is important therefore for doctors and patients to appreciate the need to detect and treat FH as early as possible.\(^6\)

In the past, the prevalence for FH was generally reported to be one in 500,\(^1\) but more recent research suggests it is more common (about one in 200 to 300),\(^7-9\) especially among populations exhibiting founder gene effects. Genetic testing has previously been the diagnostic gold standard, but it is now known that inheriting multiple less common mutations in many genes can cause similar functional consequences.\(^10\) A mutation is currently detected in 60 to 90% of individuals with FH.\(^2\) An alternative and complementary approach is to use a clinical tool such as the Dutch Lipid Clinic Network Criteria (DLCNC) score to make the diagnosis (Table),\(^11\) and this pragmatic approach is now recommended for use in the Australian primary care setting.\(^4,12\)

### Primary care based innovations

The consensus statement of the European Atherosclerosis Society and integrated guidance from the International FH Foundation is that treatment for FH should be in primary care and preferably in a family context.\(^2,6\) They advise that more complex cases and children with FH should be referred to specialist lipid or FH clinics. The Netherlands and Norway lead the way in the world for having identified the greatest proportion of individuals

---

**TABLE. DUTCH LIPID CLINIC NETWORK CRITERIA (DLCNC) FOR MAKING A CLINICAL DIAGNOSIS OF FAMILIAL HYPERCHOLESTEROLAEMIA (FH) IN ADULT INDEX CASES\(^11\)**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Family history</strong></td>
<td></td>
</tr>
<tr>
<td>First-degree relative with known premature coronary and/or vascular disease (men aged &lt;55 years, women aged &lt;60 years) OR First-degree relative with known LDL-cholesterol level above the 95th percentile for age and gender*</td>
<td>1</td>
</tr>
<tr>
<td>First-degree relative with tendinous xanthomata and/or arcus cornealis OR Children aged &lt;18 years with LDL-cholesterol level above the 95th percentile for age and gender*</td>
<td>2</td>
</tr>
<tr>
<td><strong>Clinical history</strong></td>
<td></td>
</tr>
<tr>
<td>Patients with premature coronary artery disease (men aged &lt;55 years, women aged &lt;60 years)</td>
<td>2</td>
</tr>
<tr>
<td>Patients with premature cerebral or peripheral vascular disease (men aged &lt;55 years, women aged &lt;60 years)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Physical examination</strong></td>
<td></td>
</tr>
<tr>
<td>Tendinous xanthomata</td>
<td>6</td>
</tr>
<tr>
<td>Arcus cornealis before 45 years of age</td>
<td>4</td>
</tr>
<tr>
<td><strong>Investigation</strong></td>
<td></td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/L)</td>
<td></td>
</tr>
<tr>
<td>8.5 or above</td>
<td>8</td>
</tr>
<tr>
<td>6.5 to 8.4</td>
<td>5</td>
</tr>
<tr>
<td>5.0 to 6.4</td>
<td>3</td>
</tr>
<tr>
<td>4.0 to 4.9</td>
<td>1</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td>Total</td>
</tr>
<tr>
<td>Definite FH</td>
<td>&gt;8</td>
</tr>
<tr>
<td>Probable FH</td>
<td>6 to 8</td>
</tr>
<tr>
<td>Possible FH</td>
<td>3 to 5</td>
</tr>
<tr>
<td>Unlikely FH</td>
<td>&lt;3</td>
</tr>
</tbody>
</table>

estimated to have FH, with 71% and 43% of those with FH in the two countries, respectively, estimated to have been detected. More recently, the UK has begun to improve detection and management of FH by establishing the NHS Clinical Genetics in Primary Care initiative, and also through establishing a network of regional specialist lipid clinics that are available to support primary care management.

The importance of developing an acceptable approach to increase detection and diagnosis of index cases for FH at the primary care level in Australia is partly recognised. A combined opportunistic and retrospective approach needs to be evaluated to ascertain acceptance for patients, GPs, practice nurses, nurse practitioners and practice reception staff.

Central to FH care is identification of the index case (the first individual identified with FH in a family). Data extraction tools can be used to examine the electronic medical record base in primary care practices. This can help identify patients at higher risk of FH and can be combined with family history and physical examination findings to establish a phenotypic diagnosis.

An alternative approach to detecting FH is for the laboratory to highlight opportunistically individuals at high risk of FH based on their LDL-c results. The laboratory may alert the requester that their patient is at risk of FH by adding an interpretative comment to the lipid result, which has been shown to be associated with greater reductions in LDL-c subsequently being achieved. A phone call between the chemical pathologist and the requester has been associated with significant improvements in FH detection for individuals at high risk.

The DLCNC score encompasses LDL-c concentration; family and personal history of premature coronary artery and/or vascular disease; family history of raised LDL-c; and physical examination to detect tendon xanthomata or premature arcus cornealis (Figures 1 and 2). It is important to consider and exclude secondary causes of hypercholesterolaemia, such as liver or renal disease, corticosteroid use or hypothyroidism, before making a phenotypic diagnosis of FH.

A logical next step is to initiate cascade testing of relatives of index cases to help identify those with possible FH, as half the first-degree relatives would be expected to have the condition. A subsequent shared-care approach involving support from lipid specialists and GPs can be used to help with intensive management of difficult-to-treat patients with FH.

Cascade testing

The use of cascade testing relatives of index cases (Figure 3) in the detection of FH in tertiary centres has been based on measuring plasma LDL-c levels and genetic testing, followed by treatment with statins. This is a cost-effective means to prevent CAD in an Australian setting, but fewer than 6% of all patients seen in primary care are referred for specialist care. The cost of genetic testing relatives of index cases would be prohibitive. The application of the DLCNC score to detect possible, probable and definite adult FH index cases is more feasible and cost-effective with LDL-c measurements appropriate for cascade testing children and adult relatives.

Active involvement of the primary care team (GPs, practice nurses and nurse practitioners) could improve the detection of FH in the community, but cascade testing relatives may pose significant problems. The Netherlands’ success with FH detection centred on the use of dedicated field workers to undertake family contact tracing based on index cases. The opportunities to achieve similar improvement in the Australian setting do exist, but the impact of migration coupled with vastly different population densities in the two countries need to be considered.

An integrated approach

Primary care through ease of access and frequent patient consultations offers potential to improve on current detection rates. Health promotion campaigns could increase awareness while pathology laboratory highlighting of elevated LDL-c levels together with developing family pedigrees would be useful elements for a proactive approach. Commitment from the primary care team will be vital, as imposing additional time, manpower or financial burden on practices is likely to prove unsustainable. Building the infrastructure and knowledge base from within the practice offers the best long-term option for success.

Stratification of patients with FH into low, intermediate or high complexity (see the flowchart) can help GPs determine those patients who may benefit from specialist help if needing more intensive management. The UK NICE guidelines have recognised the difficulties of undertaking cascade screening from primary care and have suggested the use of specialist lipid clinics to undertake the work instead. The DLCNC score can be employed accurately in primary care and offers a better chance of success.
Consent

Consent and collaboration from index cases to approach relatives and inform them of their risk of FH is critical in the cascade testing process. Extensive evidence shows this method to be clinically and financially effective. Approaches to perform cascade testing in primary care incorporating risk notification have been suggested.

Relatives who are also patients of the same practice as the index case should be encouraged to undertake LDL-c testing as part of their own regular health checks and advised accordingly. Other relatives, who are not patients of the practice, should ideally be advised by the index case of their potential FH risk and have LDL-c testing undertaken locally.

If the index case does not consent to cascade testing, the doctor should respect their decision and any subsequent disclosure of medical information should occur only in exceptional circumstances in line with local health services protocols or National Health and Medical Research Council guidelines. When families and index cases agree to co-operate, it is essential that patient privacy and autonomy are respected and information concerning the nature of FH is given so that it can be easily understood and undue concern avoided.

Similarly, consultations with relatives should involve pretest counselling to ensure such patients have a good understanding of the nature of FH. They should be given an uncomplicated explanation as to why early detection for themselves and/or their children might be undertaken as well as reasons for treatment if they are shown to have FH. It is likely that a blood test and clinical examination will be adequate to diagnose FH in primary care. Good communication skills and knowledge of the patient and their family background should make the process easier for primary care teams. Having a specific doctor and nurse with an interest and skills in FH detection and management at a particular practice is likely to improve the sustainability of this process.

Management

A strategy of combining effective patient counselling on the nature of FH and on the importance of lifelong therapy is essential. Regular patient contact can ensure good compliance with medications, diet, exercise and other lifestyle modifications. High on the list of priorities would be smoking cessation, and other family members in their immediate household should be similarly advised. Other risk factors for CAD disease, such as obesity, hypertension and diabetes, also need to be adequately controlled. Suggested treatment targets start with a 50% reduction from baseline LDL-c levels, whereas levels under 3 mmol/L and 2 mmol/L are advisable for those requiring more aggressive or intensive management.

There is increasing awareness that lipoprotein(a) [Lp(a)], an independent, inherited risk factor for CAD, may also contribute to the variability in incidence of CAD in FH. Consequently, patients with FH who have elevated Lp(a) may require more aggressive lowering of LDL-c, with aspirin indicated for those without symptomatic CAD.

Liver and kidney function tests together with creatine kinase measurement should be performed before patients commence lipid-lowering medication. Such baseline measurements are useful for future comparisons, especially if patients complain of myalgia or other symptoms subsequent to the start of statin therapy.

Rural GPs are often considerably disadvantaged by their geographical distance from specialist lipid colleagues. The use of the DLCNC score to achieve a phenotypic diagnosis can facilitate local assessment and enable risk stratification without relying on DNA genetic testing at a specialist centre. Specialist advice should be sought for patients requiring enhanced or intensive management (see the flowchart). The greater local community knowledge by GPs of index cases and their extended families facilitates cascade testing of relatives, while the construction of family pedigrees (Figure 3) can help increase broader community awareness of FH risk.

Women of childbearing age with FH should be adequately counselled about the risks of statin treatment in pregnancy, and advised to stop this therapy for at least three months before conception. For patients with FH who are at a particularly increased risk of CVD, the advice of a lipid specialist or cardiologist should be sought to enable a more comprehensive assessment to be undertaken.

In children and adolescents, a key focus should be a low saturated fat, heart-healthy diet.
diet; exercise; and lifestyle modifications, especially avoidance of smoking. Risk stratification can help with approaches to treatment but the importance and need for lifetime treatment must be stressed and reinforced. Statins such as simvastatin, pravastatin and fluvastatin are licensed for use in children in Australia, but the safety and efficacy of rosuvastatin in children has not been established. Full details on age groups and approved indications are provided in each product’s prescribing information, which should be consulted. If primary care physicians have concerns about initiating statin treatment or want additional guidance for this age group, they may wish to seek advice and support from lipid specialists and/or paediatric cardiologists. As with adults, baseline measurements of liver and kidney function as well as the creatine kinase level are advisable. Other developmental aspects including growth patterns, body weight and sexual and physical maturation should also be monitored regularly.

Other siblings and first-degree relatives have a 50% chance of having FH and in such circumstances it may be possible to arrange for management and follow up of a family cluster at a specialised FH clinic either in primary care or at a tertiary clinic. For those patients requiring more intensive management, the option of expensive LDL-apheresis where available or newer medications needs to be considered and advice sought from a lipid specialist. Such patients include those who are homozygous or compound heterozygous as well as those refractory to or intolerant of cholesterol lowering medications. The management of patients with severe FH – i.e. homozygous FH or heterozygous FH with progressive CAD – should be undertaken at specialist lipid centres.

Conclusion
FH is currently under-recognised and undertreated in Australia. There is increasing interest in involving primary care teams to facilitate earlier diagnosis of index cases and to develop a sustainable approach to cascade testing relatives. The ease of access and frequent patient contact are likely to facilitate this process in primary care. Increasing awareness among GPs, nurse practitioners, practice nurses and primary care teams is likely to increase the detection rate and treatment within primary care. Newly diagnosed younger patients with FH can be assured of a normal life expectancy provided they adhere to treatment guidelines with medications and lifestyle modifications.

References
A list of references is included in the website version (www.medicinetoday.com.au) and the iPad app version of this article.

ACKNOWLEDGEMENT: The authors thank Ms Jacqueline Ryan, nurse practitioner at the School of Medicine and Pharmacology, University of Western Australia, for help in the preparation of this article.

COMPETING INTERESTS: None.

ONLINE CPD JOURNAL PROGRAM
Familial hypercholesterolaemia is an autosomal dominant inherited disorder of lipid metabolism. True or false?

Review your knowledge of this topic and earn CPD points by taking part in MedicineToday’s Online CPD Journal Program. Log in to www.medicinetoday.com.au/cpd
Familial hypercholesterolaemia
Challenges in primary care

TOM BRETT MA, MD, FRACGP, MRCGP, MICGP; GERALD F. WATTS DSc, PhD, MD, FRCP, FRACP; JACQUIE GARTON-SMITH FRACGP; DAMON A. BELL FRACP, FRCPA; ALISTAIR W. VICKERY FRACP; JING PANG PhD; DIANE ARNOLD-REED PhD

References