



The Cardiac Society of Australia and New Zealand

## Guidelines for the Diagnosis and Management of Familial Hypercholesterolaemia

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### 1. Clinical Characteristics

#### 1.1 Definition and prevalence

Familial hypercholesterolaemia (FH) is a dominantly inherited condition that is due to a genetic defect in one of several genes that affect receptor-mediated uptake of low density lipoprotein (LDL) (see “Molecular Genetics” below). Affected individuals suffer metabolic and clinical features (Table 1) that include impaired uptake of plasma LDL cholesterol, resulting in high cholesterol levels and increased risk of premature cardiovascular disease.

Offspring of FH patients will inherit either the normal gene or the defective gene, so the prevalence within that branch of the family will be approximately 50%. This leads to quite a high prevalence in the general population. Estimates range between 1:200 and 1:500, but some groups exhibit a “founder gene effect” that enriches the prevalence of the disorder. It is more common in Mediterranean countries, Christian Lebanese, French Canadians and Afrikaaner South Africans. In these populations the prevalence may exceed 1:100. Homozygous cases are more common in consanguineous families, and, as with compound heterozygous cases, the increased severity of hypercholesterolaemia in these cases exacerbates premature mortality. The prevalence of homozygous FH is around 1:1 million in the general population. The detection and treatment rates of FH remain low worldwide.

#### 1.2 Clinical presentation

Index cases of FH present with one or more of the following features:

- 1) Severe hypercholesterolaemia that is not explained by secondary causes,
- 2) A strong personal or family history of premature atherosclerotic cardiovascular disease (CVD),
- 3) Tendon Xanthomas.

Relative hypercholesterolaemia is present from birth, but levels rise with age, so diagnosis should be based on LDL-C or non-HDL cholesterol (NHDLC) levels and comparison with age and gender-adjusted reference values. Females are protected from atherosclerotic disease prior to menopause, so the natural history of premature vascular disease is delayed by about one decade in women. However, the onset of CVD is accelerated by about 2 decades in both males and females. Additional metabolic and clinical features of FH are listed below.

**Table 1: Additional metabolic and clinical features of FH**

*Metabolic Features*

Increased LDL

Increased remnants including LDL's precursor, IDL

*Clinical Features*

Premature CHD

Premature CVD

Aortic stenosis

Tendon xanthomas (11%)

Corneal arcus (27%)

Xanthelasmas (12%)

Clearly there are many other potential causes of premature CVD and aortic stenosis. Likewise, corneal arcus and xanthelasma are non-specific signs. However, arcus in a young adult is suggestive of FH. Tendon xanthomas, which may gradually develop in Achilles tendons and extensor tendons on the dorsum of the hand, are pathognomonic for FH, but they may be confounded by tendon injury, and they are rarely identifiable before adulthood. With the rising tide of obesity, more patients with FH present with features of the metabolic syndrome and type 2 diabetes, which compound the risk of CVD.

### 1.3 Clinical diagnosis

Diagnosis of an index case depends on recognition of the relevant clinical features. Although the serum cholesterol level shows a moderate degree of overlap between patients with and without FH, the presence of an elevated level in a member of an affected family is suggestive of FH, particularly in the case of younger relatives. Other affected individuals can usually be identified on the basis of LDL-C levels, but studies suggest that a misdiagnosis rate of approximately 15% may apply. Several sets of diagnostic criteria have been developed, including:

**a) Dutch Lipid Clinic criteria:**

8 points	DNA Mutation, or LDL-C > 8.5
6 points	Tendon xanthomas
5 points	LDL-C 6.5 – 8.4
4 points	Arcus senilis < 45 yrs
3 points	LDL 5.0 – 6.4
2 points	Xanthomas or premature arcus in 1 <sup>st</sup> degree relative, childhood LDL > 95 <sup>th</sup> percentile, or premature CHD
1 point	1st deg relative with premature CVD or LDL > 95 <sup>th</sup> percentile, personal history of LDL 4.0 – 4.9 or premature CVD

**Definite: > 8 points**

**Probable: 6 – 8 points**

**Possible FH: 3-5 points**

or

### b) Modified UK (Simon Broome) criteria

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1. DNA Mutation
2. Tendon xanthomas in patient or 1<sup>st</sup> /2<sup>nd</sup> degree relative
3. Family history MI <50 in 2<sup>nd</sup> degree or <60 in 1<sup>st</sup> degree relative
4. Family history of cholesterol >7.5 in 1<sup>st</sup> or 2<sup>nd</sup> deg relative
5. Cholesterol >7.5 (adult) or >6.7 (age <16)
6. LDL-C >4.9 (adult) or >4.0 (age <16)

**Definite: (5 or 6) + 1**

**Probable: (5 or 6) + 2**

**Possible FH: (5 or 6) + (3 or 4)**

Both diagnostic tools are comparable in predicting mutation positive FH. Index patients with FH should be sought amongst patients presenting to cardiology and stroke units with premature CVD (aged < 60 yr), and in primary care amongst those with a family history of hypercholesterolaemia and premature CVD. We consider that all potential cases of FH should be referred to a lipid clinic / genetic service for confirmation of diagnosis, risk assessment, initial management and cascade screening or predictive testing of first-degree relatives. Risk factor counting, non-invasive testing for atherosclerosis (carotid ultrasonography, cardiac CT) and documented CVD should be used to stratify patients for routine, enhanced and high intensity treatment. Poor understanding and lack of infrastructure among physicians, patients and the community remains a key barrier to detection and effective management of FH.

## 2. Molecular Genetics

Although the clinical picture of FH will be clear-cut in many instances, the diagnostic criteria suggest that genetic testing can provide certainty of diagnosis in some cases where confounding factors such as borderline cholesterol levels, inconclusive family histories or tendon injuries have resulted in a diagnostic dilemma. The major value in making a molecular diagnosis is its use in predictive testing of other family members for FH. This is useful in early detection of cases that need intervention to prevent CVD and in re-assuring family members who may not have the condition. Individuals in whom predictive genetic tests are required should be offered genetic counselling prior to consenting to sample collection for genetic analysis. Genetic counsellors can work effectively when integrated into the FH service run out of a lipid clinic. Life insurance companies cannot insist that patients have a genetic test, but they can ask for information about the patient's medical and family history as well as the results of any tests, including lipid levels and genetic investigations, that have been performed prior to obtaining an insurance policy.

### 2.1 FH disease genes

FH may be caused by mutation in any of several genes affecting receptor-mediated uptake of LDL, including the genes for the LDL receptor, the LDL receptor ligand (apolipoprotein B100), and a protease known as Proprotein Convertase Subtilisin Kexin 9 (PCSK-9). A recessive form of FH due to a defect in the ARH gene for a chaperone protein, and the recessive disorder sitosterolaemia are sometimes grouped with FH. More importantly, FH has been described in association with over 1000 mutations of the LDL receptor gene. As a result, attempted genetic diagnosis in an index case may require extensive mutation detection studies.

## 2.2 Genetic screening

The process of trying to detect a genetic abnormality de novo is expensive and time-consuming, and failure to find a mutation is inconclusive. Nevertheless, next generation sequencing techniques for FH have been validated, and these new techniques may improve the yield. The diagnostic yield of DNA testing is directly proportional to the phenotypic certainty of FH. A protocol employed in The FHWA Programme detected a causative mutation in over 80% of cases with a definite clinical diagnosis of FH by Dutch criteria. Once a mutation has been identified within a family, the process of confirming the presence or absence of that specific mutation in individual family members is much more straightforward. See further information below if you would like more details about genetic testing for FH. DNA testing for FH is cost-effective and accordingly is now provided as a clinical service in pathology departments in Sydney, Perth and Christchurch.

## 3. Management

### 3.1 Affected individuals

FH Australasia (previously a subcommittee of the Australian Atherosclerosis Society) has developed a comprehensive “Model of Care” which has become a template for other international recommendations. The Australian guidelines are compatible, but more detailed than the UK NICE and other European guidelines for FH. Models that are integrated into primary care are required, given that the majority of well controlled FH patients should be managed in the long-term by their family doctor.

In view of the high risk of premature cardiovascular disease, regular review of clinical symptoms and signs of CVD should be undertaken. Exercise stress testing of adults is recommended, and other forms of non-invasive testing to assist the early identification of clinically relevant atherosclerosis may become accepted practice. Diet, exercise and avoidance of smoking are mandatory, and all cardiovascular risk factors should be evaluated and treated. Consideration should be given to general measures to protect against vascular events including the use of aspirin. Detection and treatment of FH in women and children merit special consideration.

Cholesterol-lowering treatment such as the statin class of drugs provides excellent control of inherited high cholesterol levels. The statins work by reducing cholesterol synthesis in the liver. This stimulates SREBP and LDL receptor gene expression. As a result, the receptors produced by the normal gene will reduce LDL cholesterol levels. The effect of statins can be enhanced by bile acid sequestrants or cholesterol absorption inhibitors such as plant sterols or ezetimibe. Target plasma levels for LDL-cholesterol for low, intermediate and high risk FH are < 4, < 3 and < 2 mmol/L, respectively. Many patients with FH can achieve target cholesterol levels, but some may warrant additional therapy. At present this consists of niacin and/or fibrates, but novel agents such as anti-PCSK9 antibodies, apo B antisense oligonucleotides, MTP Inhibitors and CETP Inhibitors are under investigation. Medication support systems will improve adherence. Statin treatment of FH males is one of the most cost-effective medical interventions available and several lines of evidence point towards major improvements in CVD event rates and total mortality of FH patients since its introduction. The management of young FH patients is still evolving. Conservative measures that concentrate on diet, nutraceuticals and avoidance of smoking are safe and effective, but statin therapy should be contemplated for children from the most severely affected families. LDL-apheresis using any of five methods for the extracorporeal and selective removal of LDL

from plasma is indicated as indefinite therapy for homozygous and compound heterozygous FH and for heterozygotes with documented CAD who are refractory to maximal therapy. Apheresis is complex and costly and should be carried out in close collaboration with a transfusion service. Surgical procedures to ameliorate very severe hypercholesterolaemia have been superseded by therapeutic liver transplantation, especially for homozygous FH.

### 3.2 Asymptomatic family members

In view of the benefit of routine cholesterol-lowering therapy, the main management challenge in FH is case identification. The high rate of morbidity and mortality associated with the onset of CHD makes it inappropriate to wait until the onset of clinical symptoms. Family follow-up has been demonstrated to be an extremely cost-effective form of case detection but, unfortunately, it is often overlooked for a variety of reasons. The resources required to identify and inform family members are often beyond the scope of the primary care physician. A family support association is important for advocacy, learning, sharing experiences and promoting services in the community. The first support group in Australia, was established in Western Australia, and other resources are accessible on-line as outlined below.

## 4. Further Information

*Useful contact information:*

- Heart Foundation of Australia Telephone: 1300 36 27 87
- Australian Atherosclerosis Society Familial Hypercholesterolaemia Subcommittee: <http://www.athero.org.au/fh.htm>
- Heart UK: <http://heartuk.org.uk/>
- Centre for Genetics Education: <http://www.genetics.edu.au>
- Familial Hypercholesterolaemia Support Group: <http://www.fhfamilysupportgroup.websyte.com.au/>
- Barossa Family Heart Study (includes self-assessed Dutch Lipid Clinic Network score, with GP adding presence of arcus/xanthoma): [www.barossaheart.com](http://www.barossaheart.com)
- Website of the Familial Hypercholesterolaemia Foundation (US): [www.thefhfoundation.org](http://www.thefhfoundation.org).

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