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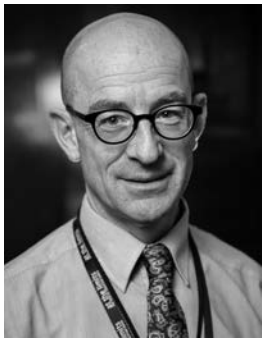

The importance of early diagnosis: how to identify patients with FH for diagnosis and referral

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Familial hypercholesterolaemia (FH) is under-diagnosed and under-treated, despite clear evidence-based guidelines for identification and management, and the availability of low-cost, generic, high-intensity statin treatment. Genetic cascade testing is the key to early diagnosis, which can help ensure that this treatment is no longer 'too little, too late'.

POINTS FOR THE CLINIC

- Cascade testing of relatives of patients with genetically confirmed FH is the most effective strategy for early identification of undiagnosed individuals
- A genetic diagnosis does not alter the treatment of FH and is required only for cascade testing in the family
- Before genetic testing is offered, patients with a provisional clinical diagnosis of FH should be referred for specialist confirmation of the clinical diagnosis
- Other inherited lipid disorders are often found in families with premature coronary artery disease and may warrant referral for specialist assessment

As outlined in the first article in this series,[1] heterozygous familial hypercholesterolaemia (HeFH) is a monogenic inherited disorder caused by a single mutation in one of three genes (*LDLR*, *APOB* and *PCSK9*) that are critical for the removal of excess low-density lipoprotein cholesterol (LDL-C) from the blood.[2] In affected individuals, serum total cholesterol (TC) and LDL-C are twice normal from birth. This results in lifelong exposure to LDL-C concentrations high enough to cause accelerated atherosclerosis even in the absence of other risk factors, all too often presenting with an early, fatal heart attack. However, as >50% reduction of LDL-C can now be achieved with high-intensity generic statin therapy (alone or in combination with second-line lipid-lowering agents), normalisation of LDL-C can be achieved in most cases. If primary prevention treatment is started early, the excess risk of premature vascular disease can effectively be eliminated. In contrast, if treatment is delayed until after the first vascular event, the benefits of preventive measures are significantly attenuated.[3] Early diagnosis is therefore of the greatest importance.

FAMILY CASCADE TESTING—THE KEY TO EARLY DIAGNOSIS

The gene alteration in HeFH is inherited as an autosomal dominant trait, which means that each first-degree relative (parents, siblings and children) has a 50% chance of also being affected (Figure 1). This knowledge provides the key to early diagnosis. As acceptance of the diagnosis and lifestyle changes is much better in children than in adolescents or young adults, the diagnosis should be made as young as possible, ideally in childhood between ages two and 10 years. This is best achieved by family cascade testing, whereby relatives are contacted with co-operation of the index case (or proband).

Before resources are committed to cascade testing within a family, a firm diagnosis must first be established and ideally confirmed by genetic testing. Although a genetic diagnostic test can be expensive, it is only required once—to identify the causative mutation in the index case in each family—and much cheaper single-mutation analysis can then be used as a 'rule in or rule out' test in family cascade testing of relatives. When a causative genetic mutation is identified and used in this way, cascade testing becomes highly efficient, as in practice at least half of first-degree relatives are found to be affected. While mutation-negative relatives can be reassured that they are unaffected, with no greater than background population risk of cardiovascular disease (CVD), each relative who carries the mutation then becomes a new index case and cascade testing can continue until all affected relatives are identified. When LDL-C is used for cascade testing the process is much less efficient, due to the overlap in LDL-C concentration in affected and unaffected relatives,[4] and more likely to break down before

all affected relatives have been identified. Family cascade testing based on genetic diagnosis is therefore more cost-effective.

An evidence-based care pathway for FH

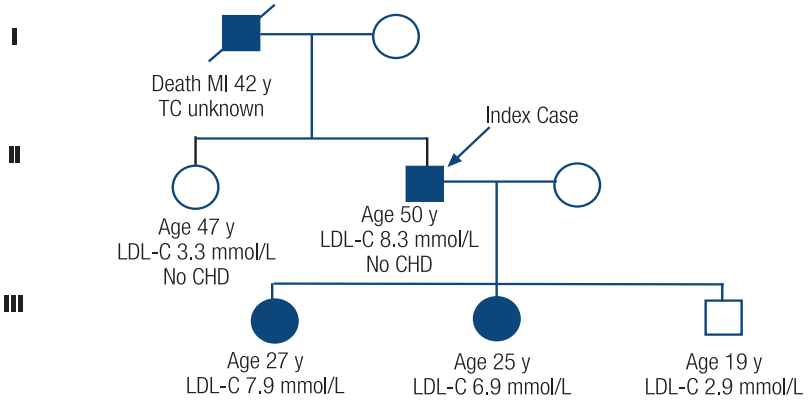
In 2008, NICE published evidence-based clinical guidelines for the identification and management of FH.[5] The key priorities from these guidelines have been summarised succinctly in the recently published FH Quality Standard,[6] five statements from which concern diagnosis, referral and cascade testing (Table 1).

In order to ensure consistent achievement of these standards, patients suspected to have FH, once identified, should enter a clearly defined care pathway agreed between primary and secondary care (Figure 2), which includes:

1. Clinical assessment and referral protocol—for entry into the FH Cascade Testing Pathway
2. DNA diagnosis (genotyping)—by comprehensive genetic analysis (CGA)
3. Cascade testing in families—based on genotype whenever possible
4. Clinical management—based on high-intensity statin therapy
5. Long-term follow-up—an annual structured review

The pathway begins with a cholesterol measurement for a routine health check or after a premature cardiovascular event in the patient or a relative.

Figure 1: Familial hypercholesterolaemia family tree showing affected members (filled symbols) in three generations



The condition was discovered when the index (arrowed) case requested a cholesterol test

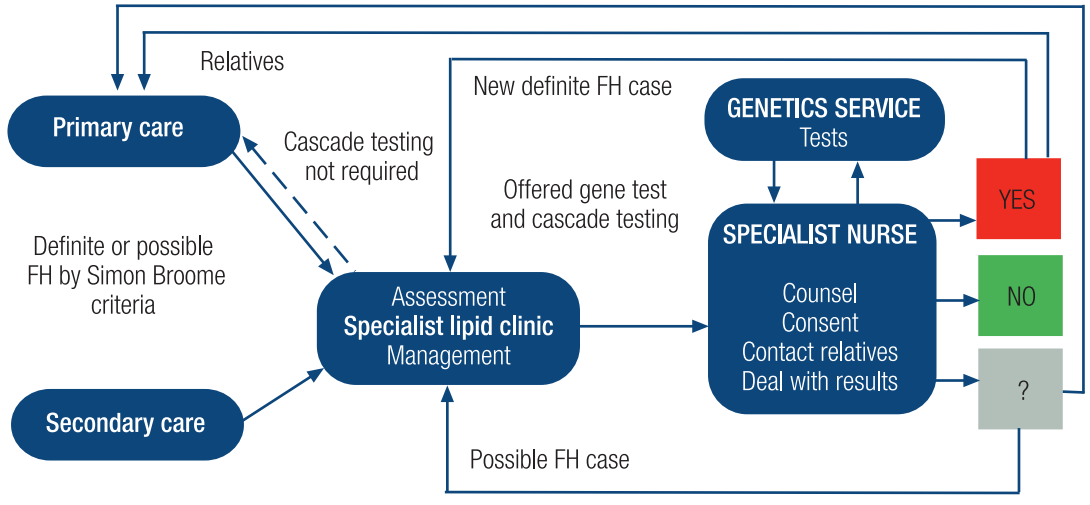
CHD = coronary heart disease; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; TC = total cholesterol

Table 1: Familial Hypercholesterolaemia (FH) Quality Statements: diagnosis, referral and cascade testing

Statement 1	Adults with a baseline total cholesterol > 7.5 mmol/l are assessed for a clinical diagnosis of familial hypercholesterolaemia (FH)
Statement 2	People with a clinical diagnosis of FH are referred for specialist assessment
Statement 3	People with a clinical diagnosis of FH are offered DNA testing as part of a specialist assessment
Statement 4	Children at risk of FH are offered diagnostic tests by the age of 10 years
Statement 5	Relatives of people with a confirmed diagnosis of monogenic FH are offered DNA testing through a nationwide, systematic cascade process

NICE Quality Standard 416: http://guidance.nice.org.uk/QS41

Figure 2: Cascade testing care pathway in familial hypercholesterolaemia



Relatives of patients with a DNA diagnosis of FH are classified affected (red) or unaffected (green) LDL-C-based cascade testing leaves one-third with uncertain status (grey) requiring follow-up

WHAT SHOULD THE GP DO?

An unexpectedly high blood cholesterol (>7.5 mmol/L, as defined by the Simon Broome criteria)[5] should certainly prompt consideration of FH. But secondary causes of hyperlipidaemia should first be excluded by review of clinical history, examination, prescribed medication and additional laboratory investigations including, as a minimum, thyroid, liver and renal functions and glycaemic status (Table 2).

Confirmation with a full fasting lipid profile including LDL-C should be arranged. The typical biochemical findings in FH are an isolated increase in TC and LDL-C with normal or even low triglyceride levels. The diagnosis is less likely if fasting triglyceride levels are persistently increased (> 2.3 mmol/L) in the absence of secondary causes.[7] Familial combined hyperlipidaemia (FCH) is more likely in such cases and is five times commoner than FH in patients presenting with premature myocardial infarction (MI),[8] although in severe cases the two conditions may coincide.[9] Other forms of inherited hyperlipidaemia are frequently found in patients with premature heart disease (<60 years) and their families (Table 3).[8]

In HeFH, serum TC and LDL-C concentrations are typically double the expected normal values, and increase with advancing age and postmenopausally in women. Therefore, while TC >7.5 mmol/L and LDL-C >4.9 mmol/L (the lipid thresholds defined by the Simon Broome criteria for consideration of FH) are strongly suggestive of HeFH in a young adult, higher concentrations are typically found in older adults with untreated HeFH (TC >9.0 mmol/L and LDL-C >6.5 mmol/L), and the higher the LDL-C, the more likely it is that the diagnosis will be confirmed on genetic testing. In a patient already on treatment with high-intensity statins before assessment, the diagnosis can be difficult, but failure to achieve LDL-C < 2.5 mmol/L (or

Table 2: Exclusion of secondary hyperlipidaemias—key investigations

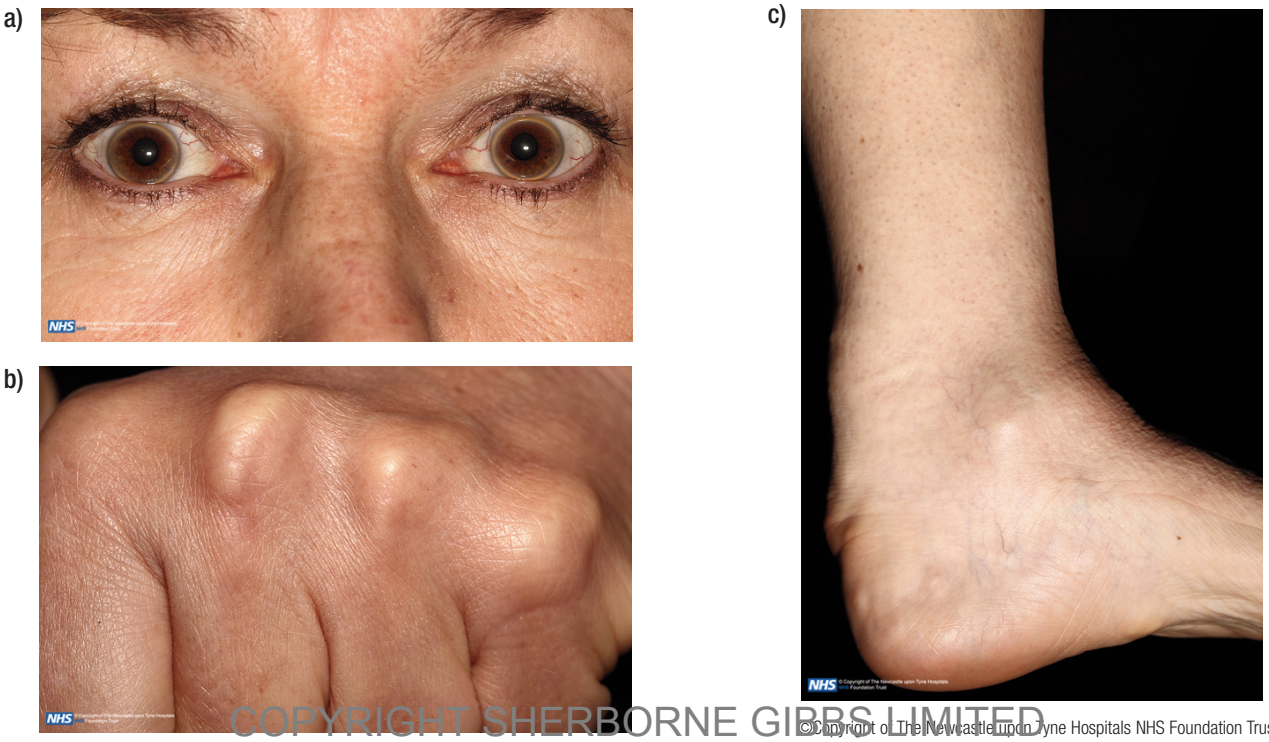
Tests	Exclude
Renal profile (Na+, K+, creatinine, eGFR)	Chronic kidney disease
Liver profile (TProt, Alb, ALP, ALT, GGT)	Cholestasis
Thyroid profile (TSH, FT4)	Hypothyroidism
Glucose (fasting) and/or HbA_{1c}	Diabetes
Dipstick urinalysis (protein)	Nephrotic syndrome

Table 3: Familial lipoprotein disorders in patients with premature coronary artery disease

Disorders	% families
Elevated lipoprotein(a)	19%
Hypertriglyceridaemia with low HDL-C	15%
Combined hyperlipidaemia	14%
Hyperapobetalipoproteinaemia	5%
Hypoalphalipoproteinaemia	4%
Hypercholesterolaemia	3%
Hypertriglyceridaemia	1%

HDL-C = high-density lipoprotein cholesterol
Adapted from Genest *et al.* 1992[8]

Figure 3: Physical signs in heterozygous FH: (a) Corneal arcus, (b) digital extensor tendon xanthoma and (c) Achilles tendon xanthoma



non-high-density lipoprotein cholesterol [HDL-C] < 2.8 mmol/L) should give rise to suspicion of an inherited lipid disorder.

A careful clinical history is important, as even apparently fit young people with HeFH may harbour significant coronary disease. Cardiovascular symptoms should be sought specifically and a baseline ECG performed if not done previously. The family history should establish the age at onset of significant cardiovascular events, most importantly confirmed CHD (MI, coronary artery bypass grafting [CABG], percutaneous coronary interventions [PCI] and/or definite coronary artery disease on angiography). A family history of MI, before age 50 years in a second-degree relative or before 60 years in a first-degree relative, is specified in the Simon Broome criteria for a diagnosis of possible FH.[5]

A thorough examination should be performed for signs of CVD, and the characteristic features of FH (Figure 3) should be sought, including careful palpation for tendon xanthomas. Although easily missed on examination, these are important to recognise, as a positive genetic diagnosis is confirmed in most patients with tendon xanthomas.[10] Xanthelasma and corneal arcus may also be found in FH patients, but only tendon xanthoma is included in the Simon Broome criteria for definite FH.[5]

WHO SHOULD BE CONSIDERED FOR DNA DIAGNOSIS AND ENTRY INTO FH CASCADE TESTING PATHWAY?

According to the NICE guidelines,[5] patients with a provisional clinical diagnosis of FH should be referred for specialist assessment and confirmation of the clinical diagnosis before genetic testing is offered. A genetic diagnosis does not influence the treatment of FH and is required only for cascade testing in the family. Where there are no known relatives (first-, second- or third-degree) eligible for testing, a clinical diagnosis is sufficient and genetic diagnosis is not required. Initiation of DNA-based family cascade testing involves the commitment of significant clinical and laboratory resources, and the specialist assessment should ensure that only appropriate cases enter the pathway.

WHAT WILL THE SPECIALIST LIPID CLINIC DO?

An accurate clinical and biochemical assessment is essential in order to confirm the clinical diagnosis of FH before genetic testing is offered. A careful review of the personal and family history, physical signs, current and previous lipid profiles and other laboratory data is essential. An autosomal dominant pattern of inheritance may become apparent when a record is made of the family tree. It is essential that the patient is given a clear explanation of the condition, how it is passed on in the family and how genetic testing can help make an early diagnosis in other family members.

The most important predictors of a positive genetic test result have been incorporated into a scoring system developed by the Dutch Lipid Clinics Network (Table 4), which can be used to prioritise cases for genetic testing.[11] A score of > 8 is considered equivalent to definite FH by the Simon Broome criteria and will be positive for a genetic mutation in the majority of cases.[7] A genetic test is warranted in suspected FH probands with a score > 6, approximately 40% of whom will be mutation-positive. However, the mutation-positive yield is significantly lower in those with scores of 3-6, and other causes of hypercholesterolaemia are then more likely; *eg* familial combined hyperlipidaemia [FCH] or polygenic hypercholesterolaemia, with or without elevated lipoprotein(a). Lipoprotein(a) should be measured once in patients with FH or a personal or family history of premature CVD.[12]

Table 4: Dutch Lipid Clinics Network criteria for diagnosis of heterozygous familial hypercholesterolaemia in adults[11]

1	**Family history**	
	I. First-degree relative with CHD and/or premature CVD*	1
	II. First-degree relative with LDL-C >5.5 mmol/l	
	III. First-degree relative with xanthoma or corneal arcus	2
	IV. First-degree relative aged <18 with LDL-C >3.9 mmol/l	
2	**Personal history**	
	I. History of premature CHD (M <55, F <60)	2
	II. History of premature PAD or CEVD	1
3	**Physical examination**	
	I. Tendon xanthomas	6
	II. Premature corneal arcus (<45 years)	4
4	**Fasting LDL-C ****	
	I. LDL-C >8.5 mmol/l	8
	II. LDL-C 6.5-8.4 mmol/l	5
	III. LDL-C 5.0-6.4 mmol/l	3
	IV. LDL-C 4.0-4.9 mmol/l	1
5	**DNA analysis**	
	I. Causative mutation in the LDLR, APOB, or PCSK9 genes	8

CEVD = cerebrovascular disease; CHD = coronary heart disease; CVD = cardiovascular disease; FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol; M = male; PAD = peripheral arterial disease; F = female

*Premature CHD and/or CVD in men <55 years, women <60 years
**LDL-C for calculation of the score is without drug treatment

Only for identification of index cases older than 18 years
Total score is the sum of the LDL-C score from Box 4 plus the highest single score from each of Boxes 1-3 plus Box 5 if available. Diagnosis of FH is 'definite' when score is > 8 points; 'probable' when score is 6-8 points; 'possible' when score is 3-5 points; 'unlikely' when score is 0-2 points

It is recommended that DNA diagnosis for FH is performed by CGA of the *LDLR*, *APOB* and *PCSK9* genes, sequencing of which is now affordable and cost-effective. This will be described in greater detail in the final article in this series.

In addition to confirmation of the diagnosis, provision of patient education and initiation of cascade testing, the specialist clinic will screen for cardiovascular complications, provide dietetic and lifestyle counselling, advise on therapeutic management and arrange an annual structured review. The management of FH will be covered in the next article in this series.

Conflicts of interest statement

The author is co-chairman of the Familial Hypercholesterolaemia Guideline Implementation Team of Heart UK and has participated in Advisory Boards for Sanofi Winthrop and Amgen on novel therapies in development for FH. The writing of this article was supported by an educational grant from Sanofi Pharmaceuticals, but the content of the article is entirely the author's own.

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