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Identification and management of familial hypercholesterolaemia

NICE clinical guideline 71

Developed by the National Collaborating Centre for Primary Care

NICE clinical guideline 71 Identification and management of familial hypercholesterolaemia

Ordering information

You can download the following documents from www.nice.org.uk/CG071

- The NICE guideline (this document) – all the recommendations.
- A quick reference guide – a summary of the recommendations for healthcare professionals.
- ‘Understanding NICE guidance’ – information for patients and carers.
- The full guideline – all the recommendations, details of how they were developed, and reviews of the evidence they were based on.

For printed copies of the quick reference guide or ‘Understanding NICE guidance’, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk and quote:

- N1640 (quick reference guide)
- N1641 (‘Understanding NICE guidance’).

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This guidance represents the view of the Institute, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer and informed by the summary of product characteristics of any drugs they are considering.

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Introduction

In some people, a high cholesterol concentration in the blood is caused by an inherited genetic defect known as familial hypercholesterolaemia (FH). A raised cholesterol concentration in the blood is present from birth and may lead to early development of atherosclerosis and coronary heart disease. The disease shows an autosomal dominant pattern of inheritance, being transmitted from generation to generation in such a way that siblings and children of a person with FH have a 50% risk of inheriting FH.

Most people with FH have inherited a defective gene for FH from only one parent and are therefore heterozygous. Rarely, a person will inherit a genetic defect from both parents and will have homozygous FH or compound heterozygous FH, which will be collectively termed homozygous FH for the purpose of this guideline.

The prevalence of heterozygous FH in the UK population is estimated to be 1 in 500, which means that approximately 110,000 people are affected. The elevated serum cholesterol concentration that characterises heterozygous FH leads to a greater than 50% risk of coronary heart disease in men by the age of 50 years and at least 30% in women by the age of 60 years.

Homozygous FH is rare, with symptoms appearing in childhood, and is associated with early death from coronary heart disease. Homozygous FH has an incidence of approximately one case per one million.

The guideline will assume that prescribers will use a drug's summary of product characteristics to inform their decisions for individual patients.

Patient-centred care

This guideline offers best practice advice on the identification and care of people with FH.

Treatment and care should take into account patients' needs and preferences. People with FH should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If patients do not have the capacity to make decisions, healthcare professionals should follow the Department of Health guidelines – 'Reference guide to consent for examination or treatment' (2001) (available from www.dh.gov.uk). Healthcare professionals should also follow a code of practice accompanying the Mental Capacity Act (summary available from www.publicguardian.gov.uk).

If the patient is under 16, healthcare professionals should follow guidelines in 'Seeking consent: working with children' (available from www.dh.gov.uk).

Good communication between healthcare professionals and patients is essential. It should be supported by evidence-based written information tailored to the patient's needs. Treatment and care, and the information patients are given about it, should be culturally appropriate. It should also be accessible to people with additional needs such as physical, sensory or learning disabilities, and to people who do not speak or read English.

If the patient agrees, families and carers should have the opportunity to be involved in decisions about treatment and care.

Families and carers should also be given the information and support they need.

Care of young people in transition between paediatric and adult services should be planned and managed according to the best practice guidance described in 'Transition: getting it right for young people' (2006) (available from www.dh.gov.uk).

Adult and paediatric healthcare teams should work jointly to provide assessment and services to young people with FH. Diagnosis and management should be reviewed throughout the transition process, and there should be clarity about who is the lead clinician to ensure continuity of care.

Key priorities for implementation

Diagnosis

- A family history of premature coronary heart disease should always be assessed in a person being considered for a diagnosis of FH (see Simon Broome criteria, appendix E).
- In children at risk of FH because of one affected parent, the following diagnostic tests should be carried out by the age of 10 years or at the earliest opportunity thereafter.
 - A DNA test if the family mutation is known.
 - LDL-C concentration measurement if the family mutation is not known. When excluding a diagnosis of FH a further LDL-C measurement should be repeated after puberty because LDL-C concentrations change during puberty.
- Coronary heart disease risk estimation tools such as those based on the Framingham algorithm should not be used because people with FH are already at a high risk of premature coronary heart disease.

Identifying people with FH using cascade testing

- Healthcare professionals should offer all people with FH a referral to a specialist with expertise in FH for confirmation of diagnosis and initiation of cascade testing (see appendix D).
- Cascade testing using a combination of DNA testing and LDL-C concentration measurement is recommended to identify affected relatives of those index individuals with a clinical diagnosis of FH. This should include at least the first- and second- and, when possible, third-degree biological relatives.
- The use of a nationwide, family-based, follow-up system is recommended to enable comprehensive identification of people affected by FH.

Management

Adults

- Healthcare professionals should consider prescribing a high-intensity statin to achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline (that is, LDL-C concentration before treatment).

Children and young people

- Healthcare professionals should offer all children and young people diagnosed with, or being investigated for, a diagnosis of FH a referral to a specialist with expertise in FH in children and young people. This should be in an appropriate child/young person-focused setting that meets the standards within the 'National service framework for children, young people and maternity services' (available from www.dh.gov.uk).

Information needs and support

Information and counselling on contraception for women and girls with FH

- When lipid-modifying drug therapy is first considered for women and girls, the risks for future pregnancy and the fetus while taking lipid-modifying drug therapy should be discussed. This discussion should be revisited at least annually.

Ongoing assessment and monitoring

Review

- All people with FH should be offered a regular structured review that is carried out at least annually.

1 Guidance

The following guidance is based on the best available evidence. The full guideline (www.nice.org.uk/CG071FullGuideline) gives details of the methods and the evidence used to develop the guidance.

Unless otherwise indicated, recommendations are relevant for people with possible or definite familial hypercholesterolaemia (FH). Recommendations are also applicable to people with heterozygous or homozygous FH, unless otherwise indicated.

1.1 *Diagnosis*

See also section 1.4 on 'Information needs and support'.

- 1.1.1 Healthcare professionals should consider the possibility of FH in adults with raised cholesterol (total cholesterol typically greater than 7.5 mmol/l), especially when there is a personal or a family history of premature coronary heart disease.
- 1.1.2 Healthcare professionals should exclude secondary causes of hypercholesterolaemia before a diagnosis of FH is considered.
- 1.1.3 A diagnosis of FH should be made using the Simon Broome criteria, which include a combination of family history, clinical signs (specifically tendon xanthomata), cholesterol concentration and DNA testing (see appendix E).
- 1.1.4 Healthcare professionals should inform people with a diagnosis of FH based on the Simon Broome criteria (see appendix E) that they have a clinical diagnosis of FH.
- 1.1.5 Healthcare professionals should consider a clinical diagnosis of homozygous FH in adults with a low-density lipoprotein cholesterol (LDL-C) concentration greater than 13 mmol/l and in children/young people with an LDL-C concentration greater than 11 mmol/l. All

people with a clinical diagnosis of homozygous FH should be offered referral to a specialist centre.

- 1.1.6 To confirm a diagnosis of FH, healthcare professionals should undertake two measurements of LDL-C concentration because biological and analytical variability occurs.
- 1.1.7 Healthcare professionals should be aware that the absence of clinical signs (for example, tendon xanthomata) in adults and children/young people does not exclude a diagnosis of FH.
- 1.1.8 A family history of premature coronary heart disease should always be assessed in a person being considered for a diagnosis of FH (see Simon Broome criteria, appendix E).
- 1.1.9 When considering a diagnosis of FH, healthcare professionals with expertise in FH should use standardised pedigree terminology to document, when possible, at least a three-generation pedigree. This should include relatives' age of onset of coronary heart disease, lipid concentrations and smoking history. For deceased relatives, the age and cause of death, and smoking history should be documented. If possible, the index individual should verify this information with other family members.
- 1.1.10 Ultrasonography of the Achilles tendon is not recommended in the diagnosis of FH.
- 1.1.11 Coronary heart disease risk estimation tools such as those based on the Framingham algorithm should not be used because people with FH are already at a high risk of premature coronary heart disease.
- 1.1.12 Healthcare professionals should offer people with a clinical diagnosis of FH a DNA test to increase the certainty of their diagnosis and to aid diagnosis among their relatives.

- 1.1.13 Healthcare professionals should inform all people who have an identified mutation diagnostic of FH that they have an unequivocal diagnosis of FH even if their LDL-C concentration does not meet the diagnostic criteria (see appendix E).
- 1.1.14 In a family where a DNA mutation is identified, not all family members may have inherited the mutation. When DNA testing has excluded FH in a member of a family, healthcare professionals should manage the person's coronary heart disease risk as in the general population¹.
- 1.1.15 In children at risk of FH because of one affected parent, the following diagnostic tests should be carried out by the age of 10 years or at the earliest opportunity thereafter.
- A DNA test if the family mutation is known.
 - LDL-C concentration measurement if the family mutation is not known. When excluding a diagnosis of FH a further LDL-C measurement should be repeated after puberty because LDL-C concentrations change during puberty.
- 1.1.16 In children at risk of homozygous FH because of two affected parents or because of the presence of clinical signs, for example, cutaneous lipid deposits (xanthomata), LDL-C concentration should be measured before the age of 5 years or at the earliest opportunity thereafter. If the LDL-C concentration is greater than 11 mmol/l then a clinical diagnosis of homozygous FH should be considered.

¹ 'Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease' (NICE clinical guideline 67). NICE clinical guideline 71 – Identification and management of familial hypercholesterolaemia

1.2 *Identifying people with FH using cascade testing*

- 1.2.1 Healthcare professionals should use systematic methods (that is, cascade testing) for the identification of people with FH.
- 1.2.2 Healthcare professionals should offer all people with FH a referral to a specialist with expertise in FH for confirmation of diagnosis and initiation of cascade testing.
- 1.2.3 Healthcare professionals with expertise in FH should explain what is meant by cascade testing, and discuss its implications with all people with FH.
- 1.2.4 Cascade testing using a combination of DNA testing and LDL-C concentration measurement is recommended to identify affected relatives of those index individuals with a clinical diagnosis of FH. This should include at least the first- and second- and, when possible, third-degree biological relatives.
- 1.2.5 In families in which a mutation has been identified, the mutation and not LDL-C concentration should be used to identify affected relatives. This should include at least the first- and second- and, when possible, third-degree biological relatives.
- 1.2.6 In the absence of a DNA diagnosis, cascade testing using LDL-C concentration measurements should be undertaken to identify people with FH.
- 1.2.7 To diagnose FH in relatives of an index individual, the gender- and age-specific criteria for LDL-C concentration in appendix E should be used. The Simon Broome LDL-C criteria for index individuals should not be used because this will result in under diagnosis.
- 1.2.8 The use of a nationwide, family-based, follow-up system is recommended to enable comprehensive identification of people affected by FH.

- 1.2.9 Healthcare professionals should be aware of the latest guidance on data protection when undertaking cascade testing.

1.3 *Management*

1.3.1 Drug treatment

Adults

- 1.3.1.1 When offering lipid-modifying drug therapy to adults with FH, healthcare professionals should inform the person that this treatment should be lifelong.
- 1.3.1.2 Statins should be the initial treatment for all adults with FH.
- 1.3.1.3 Healthcare professionals should consider prescribing a high-intensity statin to achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline (that is, LDL-C concentration before treatment).
- 1.3.1.4 The dose of statin should be increased to the maximum licensed or tolerated dose to achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline (that is, LDL-C concentration before treatment).
- 1.3.1.5 Healthcare professionals should offer treatment with a statin with a low acquisition cost for adults with FH in whom the diagnosis is made after the age of 60 and who do not have coronary heart disease.

- 1.3.1.6 Ezetimibe monotherapy is recommended as an option for the treatment of adults with heterozygous-familial hypercholesterolaemia who would otherwise be initiated on statin therapy but who are unable to do so because of contraindications to initial statin therapy².
- 1.3.1.7 Ezetimibe monotherapy is recommended as an option for the treatment of adults with heterozygous-familial hypercholesterolaemia who are intolerant to statin therapy (as defined in recommendation 1.3.1.11)².
- 1.3.1.8 Ezetimibe, coadministered with initial statin therapy, is recommended as an option for the treatment of adults with heterozygous-familial hypercholesterolaemia who have been initiated on statin therapy when²:
- serum total or LDL-C concentration is not appropriately controlled (as defined in recommendation 1.3.1.10) either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance to the initial statin therapy (as defined in recommendation 1.3.1.11)
- and
- consideration is being given to changing from initial statin therapy to an alternative statin.
- 1.3.1.9 When the decision has been made to treat with ezetimibe coadministered with a statin, ezetimibe should be prescribed on the basis of lowest acquisition cost².
- 1.3.1.10 For the purposes of this guidance, appropriate control of cholesterol concentrations should be based on individualised risk assessment in accordance with national guidance on the

² These recommendations are from 'Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia' (NICE technology appraisal guidance 132). They have been incorporated into this guideline in line with NICE procedures for developing clinical guidelines.

management of cardiovascular disease for the relevant populations³.

- 1.3.1.11 For the purposes of this guidance, intolerance to initial statin therapy should be defined as the presence of clinically significant adverse effects from statin therapy that are considered to represent an unacceptable risk to the patient or that may result in compliance with therapy being compromised. Adverse effects include evidence of new-onset muscle pain (often associated with levels of muscle enzymes in the blood indicative of muscle damage), significant gastrointestinal disturbance or alterations of liver function tests³.
- 1.3.1.12 Prescribing of drug therapy for adults with homozygous FH should be undertaken within a specialist centre.
- 1.3.1.13 Healthcare professionals should offer adults with FH a referral to a specialist with expertise in FH if treatment with the maximum tolerated dose of a high-intensity statin and ezetimibe does not achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline (that is, LDL-C concentration before treatment).
- 1.3.1.14 Healthcare professionals should offer adults with FH a referral to a specialist with expertise in FH for consideration for further treatment if they are assessed to be at very high risk of a coronary event, that is, if they have any of the following.
- Established coronary heart disease.
 - A family history of premature coronary heart disease.
 - Two or more other cardiovascular risk factors (for example, they are male, they smoke, or they have hypertension or diabetes).

³ These recommendations are from 'Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia' (NICE technology appraisal guidance 132). They have been incorporated into this guideline in line with NICE procedures for developing clinical guidelines.

- 1.3.1.15 Adults with FH with intolerance or contraindications to statins or ezetimibe should be offered a referral to a specialist with expertise in FH for consideration for treatment with either a bile acid sequestrant (resin), nicotinic acid, or a fibrate to reduce their LDL-C concentration.
- 1.3.1.16 The decision to offer treatment with a bile acid sequestrant (resin), nicotinic acid or a fibrate in addition to initial statin therapy should be taken by a specialist with expertise in FH.
- 1.3.1.17 Healthcare professionals should exercise caution when adding a fibrate or nicotinic acid to a statin because of the risk of muscle-related side effects (including rhabdomyolysis). Gemfibrozil and statins should not be used together.
- 1.3.1.18 Adults with FH who are prescribed nicotinic acid should be offered advice on strategies that reduce flushing. Such advice should include taking low initial doses with meals and/or aspirin 30 minutes before the first daily dose.

Children and young people

- 1.3.1.19 Healthcare professionals should offer all children and young people diagnosed with, or being investigated for, a diagnosis of FH a referral to a specialist with expertise in FH in children and young people. This should be in an appropriate child/young person-focused setting that meets the standards within the 'National service framework for children, young people and maternity services' (available from www.dh.gov.uk).
- 1.3.1.20 Lipid-modifying drug therapy for a child or young person with FH should usually be considered by the age of 10 years. The decision to defer or offer lipid-modifying drug therapy for a child or young person should take into account:
- their age
 - the age of onset of coronary heart disease within the family, and

- the presence of other cardiovascular risk factors, including their LDL-C concentration.
- 1.3.1.21 When offering lipid-modifying drug therapy for children or young people, healthcare professionals should inform the child/young person and their parent/carer that this treatment should be lifelong.
- 1.3.1.22 When the decision to initiate lipid-modifying drug therapy has been made in children and young people, statins should be the initial treatment. Healthcare professionals with expertise in FH in children and young people should choose a statin that is licensed for use in the appropriate age group.
- 1.3.1.23 Statin therapy for children and young people with FH should usually be prescribed at the doses specified in the 'British national formulary (BNF) for children'.
- 1.3.1.24 In exceptional instances, for example, when there is a family history of coronary heart disease in early adulthood, healthcare professionals with expertise in FH in children and young people should consider offering:
- a higher dose of statin than is licensed for use in the appropriate age group, and/or
 - more than one lipid-modifying drug therapy, and/or
 - lipid-modifying drug therapy before the age of 10 years.
- 1.3.1.25 In children and young people with homozygous FH, LDL-C concentration may be lowered by lipid-modifying drug therapy and this should be considered before LDL apheresis (see section 1.3.3).
- 1.3.1.26 In children and young people with FH who are intolerant of statins, healthcare professionals should consider offering other lipid-modifying drug therapies capable of reducing LDL-C concentration (such as bile acid sequestrants [resins], fibrates or ezetimibe).

1.3.1.27 Routine monitoring of growth and pubertal development in children and young people with FH is recommended.

Adults and children/young people

1.3.1.28 Decisions about the choice of treatment should be made following discussion with the adult or child/young person and their parent/carer, and be informed by consideration of concomitant medication, comorbidities, safety and tolerability.

1.3.1.29 Healthcare professionals should consider offering fat-soluble vitamin (vitamins A, D and K) and folic acid supplementation for adults or children/young people with FH who are receiving long-term treatment with bile acid sequestrants (resins).

1.3.1.30 Healthcare professionals should offer people with FH a referral to a specialist with expertise in FH if they are experiencing side effects that compromise concordance with lipid-modifying drug therapy.

1.3.1.31 When the decision has been made to offer adults or children/young people with FH treatment with a statin, baseline liver and muscle enzymes (including transaminases and creatine kinase, respectively) should be measured before initiation of therapy. However, people with raised liver or muscle enzymes should not routinely be excluded from statin therapy.

1.3.1.32 Routine monitoring of creatine kinase is not recommended in asymptomatic adults or children/young people with FH who are receiving treatment with a statin.

1.3.2 Lifestyle interventions

1.3.2.1 Healthcare professionals should regard lifestyle advice as a component of medical management, and not as a substitute for lipid-modifying drug therapy.

Diet

1.3.2.2 All people with FH should be offered individualised nutritional advice from a healthcare professional with specific expertise in nutrition.

1.3.2.3 People with FH should be advised to consume a diet in which:

- total fat intake is 30% or less of total energy intake
- saturated fats are 10% or less of total energy intake
- intake of dietary cholesterol is less than 300 mg/day
- saturated fats are replaced by increasing the intake of monounsaturated and polyunsaturated fats.

It may be helpful to suggest they look at

www.eatwell.gov.uk/healthydiet for further practical advice.

1.3.2.4 Healthcare professionals should advise people with FH to eat at least five portions of fruit and vegetables a day, in line with national guidance for the general population. Examples of what constitutes a portion can be found at www.eatwell.gov.uk/healthydiet and www.5aday.nhs.uk.

1.3.2.5 Healthcare professionals should advise people with FH to consume at least two portions of fish a week (one of which should be oily fish). Pregnant women with FH should be advised to limit their oily fish to two portions a week. Further information and advice on healthy cooking methods can be found at www.eatwell.gov.uk/healthydiet.

1.3.2.6 Healthcare professionals should advise people with FH that if they wish to consume food products containing stanols and sterols these need to be taken consistently to be effective.

1.3.2.7 People with FH should not routinely be recommended to take omega-3 fatty acid supplements. For people with FH who have

already had a myocardial infarction (MI), refer to 'MI: secondary prevention' (NICE clinical guideline 48).

Physical activity

- 1.3.2.8 Healthcare professionals should advise people with FH to take at least 30 minutes of physical activity a day, of at least moderate intensity, at least 5 days a week, in line with national guidance for the general population⁴.
- 1.3.2.9 Healthcare professionals should encourage people with FH who are unable to perform moderate-intensity physical activity at least 5 days a week because of comorbidity, disability, medical conditions or personal circumstances to exercise at their maximum safe capacity.
- 1.3.2.10 Recommended types of physical activity include those that can be incorporated into everyday life, such as brisk walking, using stairs and cycling⁴.
- 1.3.2.11 Healthcare professionals should advise people with FH that bouts of physical activity of 10 minutes or more accumulated throughout the day are as effective as longer sessions⁴.

Weight management

- 1.3.2.12 Healthcare professionals should offer people with FH who are overweight or obese appropriate advice and support to achieve and maintain a healthy weight in line with NICE guidance on obesity⁵.

Alcohol consumption

- 1.3.2.13 As for the general population, alcohol consumption for adult men with FH should be limited to up to 3–4 units a day, and for adult women with FH up to 2–3 units of alcohol a day. Binge drinking

⁴ See 'At least five a week: evidence on the impact of physical activity and its relationship to health. A report from the Chief Medical Officer' (2004), available from www.dh.gov.uk.

⁵ 'Obesity: guidance on the prevention, identification, assessment and management of overweight and obesity in adults and children' (NICE clinical guideline 43).

should be avoided. Further information can be found at www.eatwell.gov.uk/healthydiet.

Smoking advice

- 1.3.2.14 People with FH, especially children, who do not smoke should be strongly discouraged from starting because of their already greatly increased risk of coronary heart disease.
- 1.3.2.15 People with FH who smoke should be advised that, because of their already greatly increased risk of coronary heart disease, they should stop.
- 1.3.2.16 Healthcare professionals should offer people who want to stop smoking support and advice, and referral to an intensive support service, in line with the NICE guidance on smoking cessation⁶.
- 1.3.2.17 People with FH who are unwilling or unable to accept a referral to an intensive support service should be offered pharmacotherapy in line with NICE guidance on nicotine replacement therapy and bupropion⁷, and varenicline⁸.

1.3.3 Specialist treatment

LDL-lowering apheresis

- 1.3.3.1 Healthcare professionals should consider offering LDL apheresis for the treatment of adults and children/young people with homozygous FH (see recommendations 1.1.5 and 1.1.16). The timing of initiation of LDL apheresis should depend on factors such as the person's response to lipid-modifying drug therapy and presence of coronary heart disease.
- 1.3.3.2 In exceptional instances (such as when there is progressive, symptomatic coronary heart disease, despite maximal tolerated

⁶ 'Brief interventions and referral for smoking cessation in primary care and other settings' (NICE public health intervention guidance 1).

⁷ 'Guidance on the use of nicotine replacement therapy (NRT) and bupropion for smoking cessation' (NICE technology appraisal guidance 39).

⁸ 'Varenicline for smoking cessation' (NICE technology appraisal guidance 123).

lipid-modifying drug therapy and optimal medical and surgical therapy), healthcare professionals should consider offering LDL apheresis for the treatment of people with heterozygous FH. This should take place in a specialist centre on a case-by-case basis and data recorded in an appropriate registry.

- 1.3.3.3 Healthcare professionals should recommend arterio-venous fistulae as the preferred method of access for people with FH who are offered treatment with LDL apheresis. People should be counselled about possible benefits and complications of this procedure.
- 1.3.3.4 Routine monitoring of the person's iron status should be carried out and iron supplementation initiated as required for people with FH who are receiving treatment with LDL apheresis.
- 1.3.3.5 Angiotensin-converting enzyme (ACE) inhibitors should not be used in people with FH who are being treated with LDL apheresis. Instead, ACE inhibitors should be substituted with angiotensin-receptor blocking agents.
- 1.3.3.6 People with FH who are receiving blood pressure-lowering drug therapy should have this reviewed and considered for discontinuation on the morning of the day of LDL apheresis.
- 1.3.3.7 People with FH who are taking warfarin should have this discontinued approximately 4 days before LDL apheresis and substituted with low molecular weight heparin.
- 1.3.3.8 People with FH who are receiving anti-platelet therapy should have this continued if they are receiving treatment with LDL apheresis.

Liver transplantation

- 1.3.3.9 Healthcare professionals should consider offering liver transplantation as an option for the treatment of people with homozygous FH after treatment with lipid-modifying drug therapy and LDL apheresis.

- 1.3.3.10 The decision to refer for liver transplantation should take place in partnership with the patient and/or their relatives in an appropriate specialist setting, following a discussion of the benefits and potential harms of undertaking or declining transplantation.

1.4 Information needs and support

1.4.1 General information and support

- 1.4.1.1 During the assessment and communication of familial risk, people should receive clear and appropriate educational information about FH, the process of family testing, DNA testing and the measurement of LDL-C concentration.
- 1.4.1.2 A healthcare professional with expertise in FH should provide information to people with FH on their specific level of risk of coronary heart disease, its implications for them and their families, lifestyle advice and treatment options.
- 1.4.1.3 Healthcare professionals with expertise in FH should encourage people with FH to contact their relatives to inform them of their potential risk and so that cascade testing can take place.
- 1.4.1.4 When considering cascade testing, a healthcare professional with expertise in FH should offer to facilitate the sharing of information about FH with family members.
- 1.4.1.5 Healthcare professionals should offer people with FH and their families written advice and information about patient support groups.

1.4.2 Information and counselling on contraception for women and girls with FH

- 1.4.2.1 When lipid-modifying drug therapy is first considered for women and girls, the risks for future pregnancy and the fetus while taking lipid-modifying drug therapy should be discussed. This discussion should be revisited at least annually.

1.4.2.2 Healthcare professionals should give women and girls with FH specific information tailored to their needs and should offer a choice of effective contraceptive methods.

1.4.2.3 Combined oral contraceptives (COCs) are not generally contraindicated for women and girls being treated with lipid-modifying drug therapy. However, because there is a potential small increased risk of cardiovascular events with the use of COCs, healthcare professionals should consider other forms of contraception. Prescribers should refer to the summary of product characteristics of COCs and the relevant lipid-modifying drugs for their specific contraindications.

1.4.3 Information for pregnant women with FH

1.4.3.1 Healthcare professionals should be aware that, in general, there is no reason to advise against pregnancy or breastfeeding in women with FH.

1.4.3.2 Healthcare professionals should advise women with FH that lipid-modifying drug therapy should not be taken if they are planning to conceive or during pregnancy, because of the potential risk of fetal abnormality. Women should be advised that lipid-modifying drug therapy should be stopped 3 months before they attempt to conceive.

1.4.3.3 Women with FH who conceive while taking statins or other systemically absorbed lipid-modifying drug therapy should be advised to stop treatment immediately and they should be offered an urgent referral (see appendix D) to an obstetrician for a fetal assessment. Women should be fully informed about the nature and purpose of the assessment.

1.4.3.4 Women with FH who have conceived while taking statins or other systemically absorbed lipid-modifying drug therapy and have had a fetal assessment should be given time, opportunity and full

information to consider their options (including the advantages and disadvantages) of continuing with their pregnancy.

- 1.4.3.5 Shared-care arrangements, to include expertise in cardiology and obstetrics, should be made for women with FH who are considering pregnancy or are pregnant. Such care should include an assessment of coronary heart disease risk, particularly to exclude aortic stenosis. This is essential for women with homozygous FH.
- 1.4.3.6 Serum cholesterol concentrations should not be measured routinely during pregnancy.
- 1.4.3.7 Women with FH who are pregnant should be advised on the potential risks and benefits of re-starting lipid-modifying drug therapy for the mother and breastfed infant. Resins are the only lipid-modifying drug therapy that should be considered during lactation.

1.5 Ongoing assessment and monitoring

1.5.1 Review

- 1.5.1.1 All people with FH should be offered a regular structured review that is carried out at least annually.
- 1.5.1.2 A baseline electrocardiogram (ECG) should be considered for adults with FH.
- 1.5.1.3 Healthcare professionals should record the progress of cascade testing among the relatives of a person with FH as part of the structured review. This should include at least the first- and second- and, when possible, third-degree biological relatives. If there are still relatives who have not been tested, further action should be discussed.
- 1.5.1.4 Healthcare professionals should update the family pedigree of a person with FH and note any changes in the coronary heart disease status of their relatives as part of the structured review.

This should include at least the first- and second- and, when possible, third-degree biological relatives.

- 1.5.1.5 Structured review should include assessment of any symptoms of coronary heart disease and smoking status, a fasting lipid profile, and discussion about concordance with medication, possible side effects of treatment the patient may be experiencing, and any changes in lifestyle or lipid-modifying drug therapy that may be required to achieve the recommended LDL-C concentration (see section 1.3).

1.5.2 Referral for evaluation of coronary heart disease

- 1.5.2.1 Healthcare professionals should offer people with FH an urgent referral (see appendix D) to a specialist with expertise in cardiology for evaluation if they have symptoms or signs of possible coronary heart disease which are not immediately life-threatening. A low threshold for referral is recommended.
- 1.5.2.2 A person with FH with symptoms or signs of possible coronary heart disease which are immediately life-threatening (for example, acute coronary syndrome) should be referred to hospital as an emergency in line with advice for the general population.
- 1.5.2.3 Healthcare professionals should consider offering people with FH a referral for evaluation of coronary heart disease if they have a family history of coronary heart disease in early adulthood, or two or more other cardiovascular risk factors (for example, they are male, they smoke, or they have hypertension or diabetes).
- 1.5.2.4 Upon diagnosis, healthcare professionals should offer all adults and children/young people with homozygous FH a referral for an evaluation of coronary heart disease.
- 1.5.2.5 In asymptomatic children and young people with heterozygous FH, evaluation of coronary heart disease is unlikely to detect clinically significant disease and referral should not be routinely offered.

2 Notes on the scope of the guidance

NICE guidelines are developed in accordance with a scope that defines what the guideline will and will not cover. The scope of this guideline is available from <http://guidance.nice.org.uk/page.aspx?o=406112>.

How this guideline was developed

NICE commissioned the National Collaborating Centre for Primary Care to develop this guideline. The Centre established a Guideline Development Group (see appendix A), which reviewed the evidence and developed the recommendations. An independent Guideline Review Panel oversaw the development of the guideline (see appendix B).

There is more information in the booklet: 'The guideline development process: an overview for stakeholders, the public and the NHS' (third edition, published April 2007), which is available from www.nice.org.uk/guidelinesprocess or from NICE publications (phone 0845 003 7783 or email publications@nice.org.uk and quote reference N1233).

3 Implementation

The Healthcare Commission assesses the performance of NHS organisations in meeting core and developmental standards set by the Department of Health in 'Standards for better health' (available from www.dh.gov.uk).

Implementation of clinical guidelines forms part of the developmental standard D2. Core standard C5 says that national agreed guidance should be taken into account when NHS organisations are planning and delivering care.

NICE has developed tools to help organisations implement this guidance (listed below). These are available on our website (www.nice.org.uk/CG071).

- Slides highlighting key messages for local discussion.
- Costing tools:
 - costing report to estimate the national savings and costs associated with implementation
 - costing template to estimate the local costs and savings involved.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- Audit support for monitoring local practice.

4 Research recommendations

The Guideline Development Group has made the following recommendations for research, based on its review of evidence, to improve NICE guidance and patient care in the future. The Guideline Development Group's full set of research recommendations is detailed in the full guideline (see section 5).

4.1 *Identification using clinical registers*

What is the clinical and cost effectiveness of identifying a person with FH (defined by DNA testing) from GP registers and from secondary care registers?

Why this is important

Research is needed to compare the utility of strategies other than cascade screening to identify new index cases, because currently recommended strategies are likely to lead to the identification of less than 50% of the expected number of people with FH in the UK.

These additional strategies should evaluate note searching in general practice and from secondary care coronary heart disease registers (for example, MINAP), using a 'reference standard' of known FH-causing mutations. This will require the development of different algorithms for patient identification in primary and secondary care. These algorithms should be based on the UK FH diagnostic criteria and a combination of different cut-off points for untreated raised total or LDL-C concentration, age of onset of heart disease in the index case, age of onset of heart disease in first-degree relatives, and other factors.

4.2 *Lipid-modifying drug therapy in children*

What is the clinical effectiveness and safety of differing doses of lipid-modifying therapy in children with FH?

Why this is important

There have been no published studies to establish target serum LDL-C concentration in treated children with FH receiving lipid-modifying drug therapy. Treatment is recommended from 10 years onwards, however this

lack of data prevents a recommendation regarding the aim of pharmacological treatment on serum LDL-C concentrations.

Research (both cross-sectional and longitudinal) should assess the evidence of end-organ involvement (for example, carotid intima medial thickness [IMT]) to determine at which age abnormalities can first be seen in children. The aim would be to identify a threshold effect, with an LDL-C concentration below which carotid IMT is normal and where thickening is absent, and above which it is abnormal and where thickening is observed. Outcomes should include fasting serum total and LDL-C concentration, carotid artery IMT, and growth and pubertal development.

4.3 *LDL apheresis for people with heterozygous FH*

What are the appropriate indications, effectiveness and safety of LDL apheresis in people with heterozygous FH?

Why this is important

There is limited evidence to inform specific indications for LDL apheresis in people with heterozygous FH. In addition, there is limited published evidence on the cardiovascular outcome of such patients treated with LDL apheresis.

Evidence on the value of investigations (various measures of vascular status, considered to reflect the extent or activity of atherosclerotic vascular disease of the coronary arteries) in predicting outcome from LDL apheresis should ideally be based on evidence from randomised controlled trials with clinical outcomes. It is difficult to identify a suitable alternative treatment because LDL apheresis is generally only considered in people for whom no other treatment is available. One comparator may be novel therapies with antisense oligonucleotides (ApoB).

A national register should be established for all people with FH who are referred for and/or are undergoing LDL apheresis. Data should be collected on the natural history of FH and the temporal relationship of clinical and vascular features in relation to treatments and other parameters.

4.4 *Pregnancy in women with FH*

What are the implications of FH for the safety of a mother during pregnancy and what are the risks of fetal malformations attributable to pharmacological therapies?

Why this is important

There is little information on the outcomes of pregnancy in women with FH. A small number of conflicting studies have suggested a small increase in fetal abnormalities if the mother has taken statins during the first trimester, but there are not sufficient data to provide an accurate estimate of the level of risk. There is also limited information on the risk of pregnancy (including cardiac death) in a woman with FH.

Data on the incidence of cardiac problems in pregnancy and incidence of fetal malformation would inform future recommendations. This could reduce uncertainty for women, and help to identify risks during the pregnancy that could be better managed. The only feasible research method to address these questions is an observational longitudinal study following women with FH and other women (not diagnosed with FH) using statins through their pregnancies using a national register.

4.5 *Cardiovascular evaluation for people with FH*

What is the utility of routine cardiovascular evaluation for asymptomatic people with FH?

Why this is important

Because of their inherent high risk of developing premature coronary heart disease, a low threshold of suspicion for coronary disease is recommended for people with FH. Routine monitoring to detect sub-clinical atherosclerosis should be non-invasive, sensitive, specific and cost effective. Research to assess the prevalence of both asymptomatic coronary and non-coronary atherosclerosis in people with definite heterozygous FH is required.

As well as exercise ECG testing followed by stress echocardiography before possible angiography in people with an abnormal exercise test and ankle

brachial pressure measures, research should include magnetic resonance imaging (MRI) in addition to other modalities such as carotid IMT and coronary calcification. Outcomes should include changes in exercise ECG/ankle brachial pressure testing/IMT/calcification over time.

Consideration should also be given to the feasibility of conducting a long-term randomised trial to compare the differences in morbidity or mortality attributable to early diagnosis using routine monitoring or symptom-based investigation.

5 Other versions of this guideline

5.1 Full guideline

The full guideline, 'Identification and management of familial hypercholesterolaemia (FH)', contains details of the methods and evidence used to develop the guideline. It is published by the National Collaborating Centre for Primary Care, and is available from www.rcgp.org.uk/clinical_and_research/clinical_guidelines_nccpc.aspx, our website (www.nice.org.uk/CG071fullguideline) and the National Library for Health (www.nlh.nhs.uk).

5.2 Quick reference guide

A quick reference guide for healthcare professionals is available from www.nice.org.uk/CG071quickrefguide

For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk (quote reference number N1640).

5.3 'Understanding NICE guidance'

Information for patients and carers ('Understanding NICE guidance') is available from www.nice.org.uk/CG071publicinfo

For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk (quote reference number N1641).

6 Related NICE guidance

Published

Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia. NICE technology appraisal guidance 132 (2007).

Available from www.nice.org.uk/TA132

Varenicline for smoking cessation. NICE technology appraisal guidance 123 (2007). Available from www.nice.org.uk/TA123

Statins for the prevention of cardiovascular events. NICE technology appraisal guidance 94 (2006). Available from www.nice.org.uk/TA094

Guidance on the use of nicotine replacement therapy (NRT) and bupropion for smoking cessation. NICE technology appraisal guidance 39 (2002). Available from www.nice.org.uk/TA039

Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. NICE clinical guideline 67 (2008). Available from www.nice.org.uk/CG067

MI: secondary prevention. Secondary prevention in primary and secondary care for patients following a myocardial infarction. NICE clinical guideline 48 (2007). Available from www.nice.org.uk/CG048

Obesity: guidance on the prevention, identification, assessment and management of overweight and obesity in adults and children. NICE clinical guideline 43 (2006). Available from www.nice.org.uk/CG043

Long-acting reversible contraception. NICE clinical guideline 30 (2005). Available from www.nice.org.uk/CG030

Brief interventions and referral for smoking cessation in primary care and other settings. NICE public health intervention guidance 1 (2006). Available from www.nice.org.uk/PHI001

7 Updating the guideline

NICE clinical guidelines are updated as needed so that recommendations take into account important new information. We check for new evidence 2 and 4 years after publication, to decide whether all or part of the guideline should be updated. If important new evidence is published at other times, we may decide to do a more rapid update of some recommendations.

Appendix A: The Guideline Development Group⁹

Full GDG members were:

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⁹ See the full guideline (see section 5.1) for a complete list of contributors.
NICE clinical guideline 71 – Identification and management of familial hypercholesterolaemia

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Appendix B: The Guideline Review Panel

The Guideline Review Panel is an independent panel that oversees the development of the guideline and takes responsibility for monitoring adherence to NICE guideline development processes. In particular, the panel ensures that stakeholder comments have been adequately considered and responded to. The panel includes members from the following perspectives: primary care, secondary care, lay, public health and industry.

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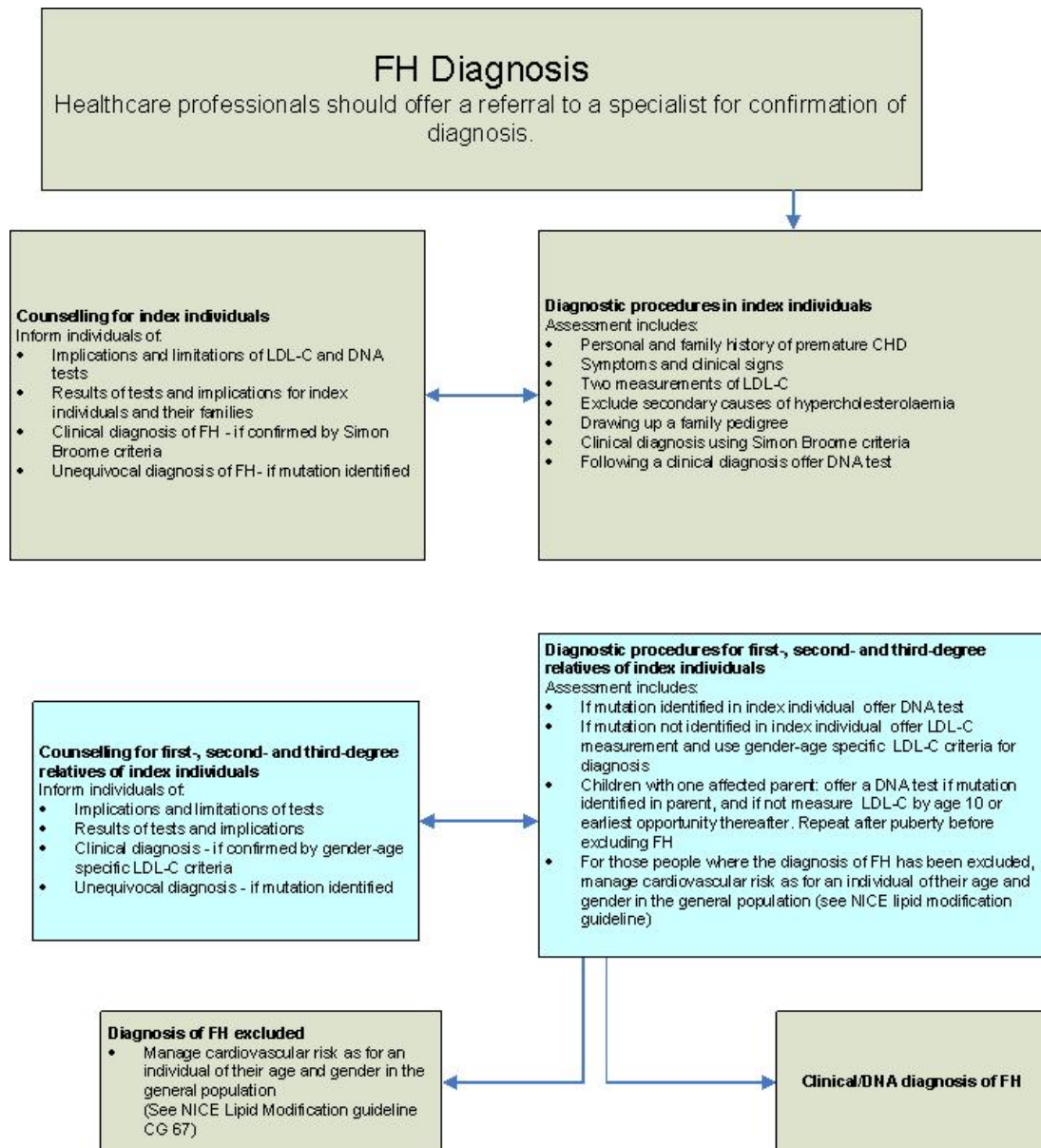
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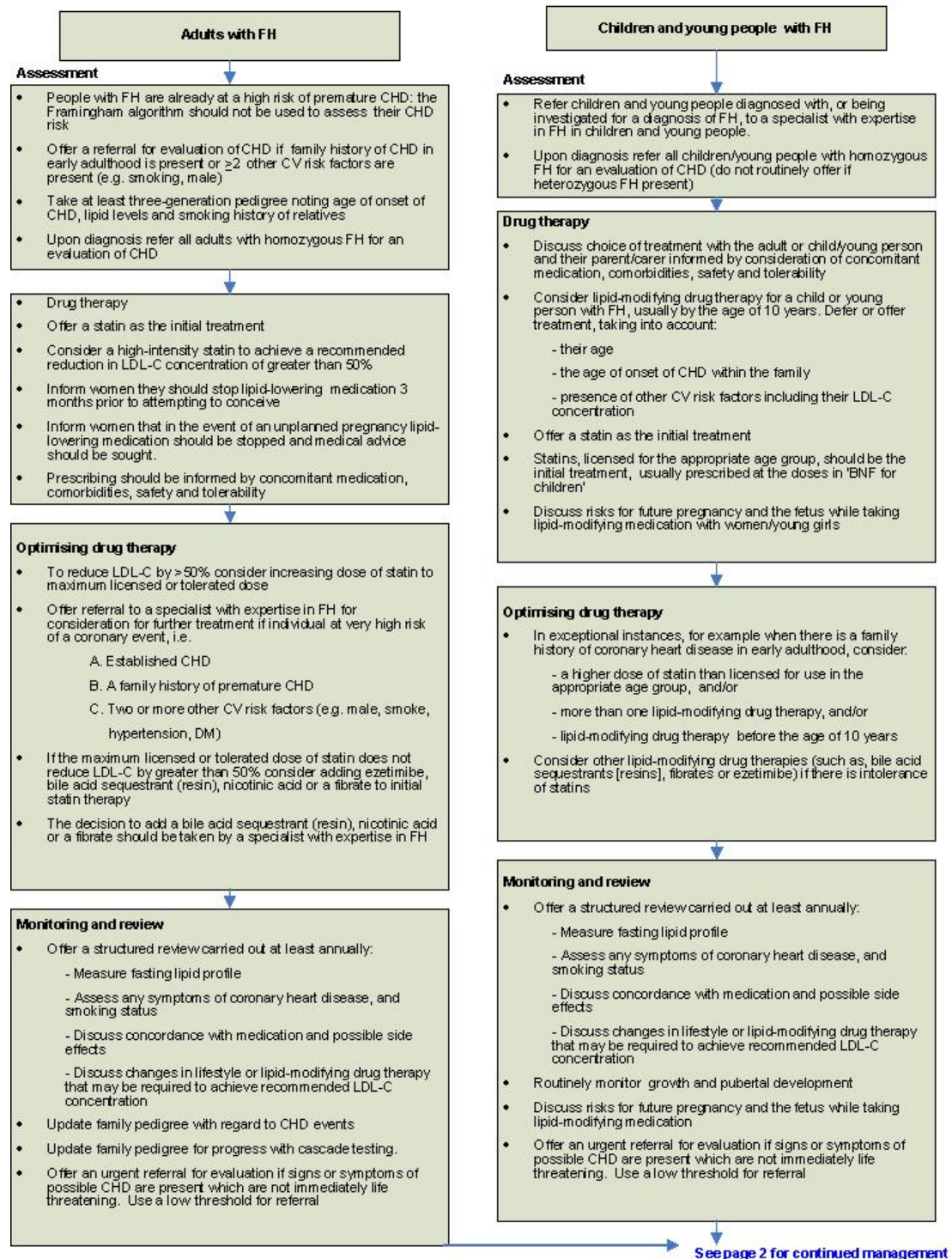
Ms Karen Cowley

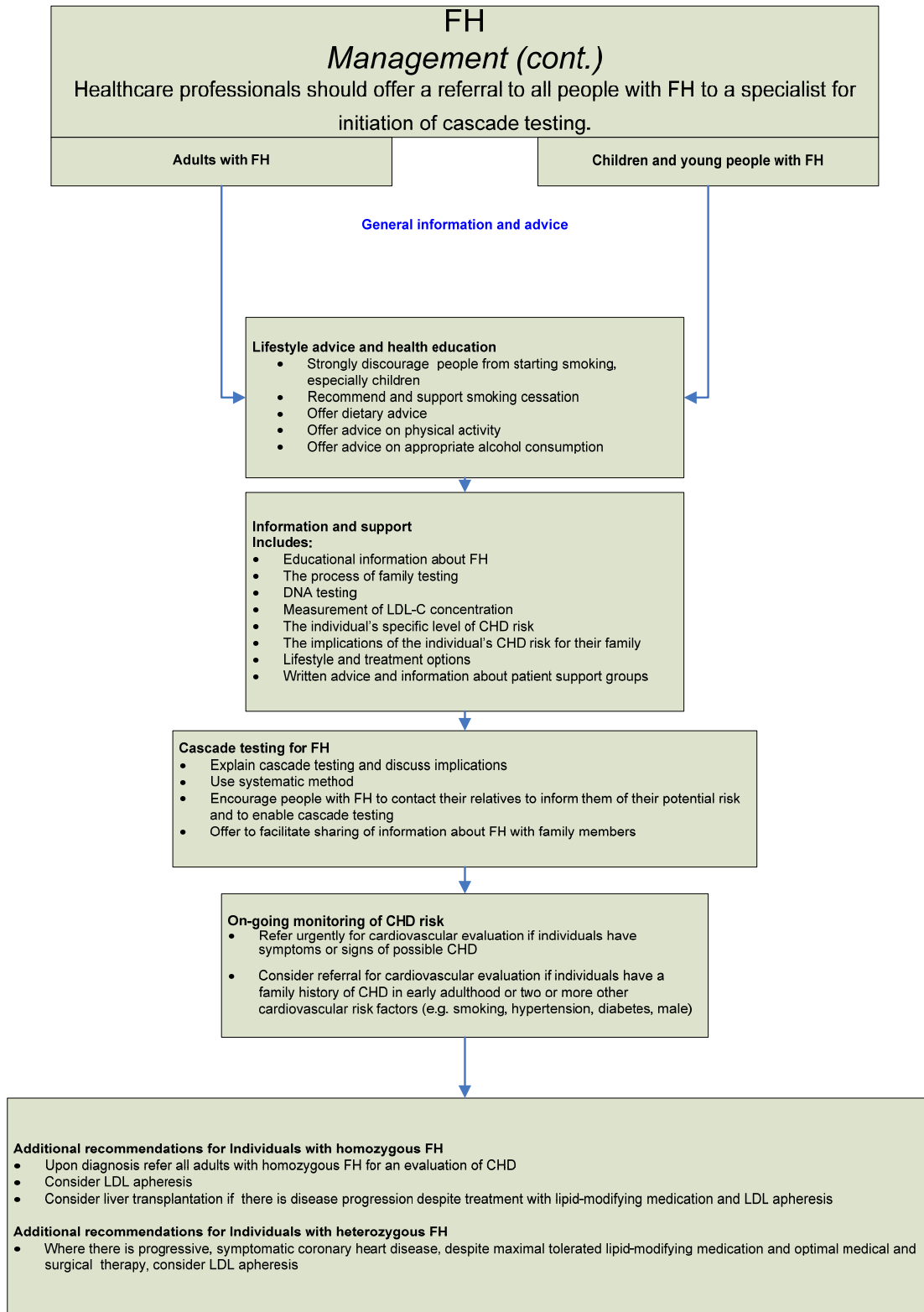
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Appendix C: The care pathways



FH Management





Appendix D: Definitions used in the guideline

Adults with FH	For the purposes of this guideline, 'adults' includes all persons with familial hypercholesterolaemia (FH; heterozygous or homozygous) who are 16 years and older.
Cascade testing	Cascade testing is a mechanism for identifying people at risk of a genetic condition by a process of family tracing. For FH the test employed is measurement of low-density lipoprotein cholesterol (LDL-C) in the blood, and/or a DNA test if a disease-causing mutation has been identified in the index individual/proband (see below).
Children/young people	For the purposes of this guideline, 'children' refers to persons younger than 10 years; 'young people' refers to persons from 10 years of age up to the age of 15 years. The definitions used here are not prescriptive and healthcare professionals are expected to exercise their judgement and consider the wishes of the patients, and their families or carers when interpreting these terms in individual instances.
Child-focused setting	Child-focused refers to valuing the child's view and validating their voice in making decisions impacting their lives. A child-focused facility or space is one designed from the viewpoint of the service recipients.
Family history	The structure and relationships within the family that relates information about diseases in family members.
First-degree relative	A person's biological parents, brothers and sisters, and children.
Heterozygous FH	High LDL-C concentration in the blood caused by an inherited mutation from one parent only. People with FH are at increased risk of cardiovascular disease.
High-intensity statin	Statins are classified as high intensity if they produce greater LDL-C reductions than simvastatin 40 mg (for example, simvastatin 80 mg and appropriate doses of atorvastatin and rosuvastatin).
Homozygous FH	<p>Very high LDL-C concentration in the blood caused by an inherited mutation from both parents. When a person inherits exactly the same affected gene from both parents this is called truly 'homozygous' FH. When the mutations in the LDL receptor gene (or equivalent) are different, this state is called 'compound heterozygous'. In general, the overall effect in both states is similar, in that LDL-C concentrations are very high. Both groups of patients have the same clinical pattern and high risk of cardiovascular disease.</p> <p>For clinical purposes, both homozygous FH and compound heterozygous FH can be regarded as behaving in a similar manner. Therefore, for the purposes of this guideline the term 'homozygous FH' is used to also encompass compound heterozygous FH.</p>
Index individual (synonymous with 'proband')	The original patient who is the starting point for follow-up of other members of a family when investigating for possible causative genetic factors of the presenting condition.
Lipid measurements/concentrations/levels	<p>These terms refer to the measurement of total cholesterol (TC), triglycerides (TGs), high-density lipoprotein cholesterol (HDL-C), and LDL-C. LDL-C is not usually measured directly but calculated from the TC, TGs and HDL-C, ideally using a fasting sample.</p> <p>Such tests are usually done in a clinical biochemistry laboratory.</p>

Mutation	An identified change in the DNA sequence of a gene that is predicted to damage the normal function of the gene and so cause disease.
Pedigree	A method of characterising the relatives of an index individual/case and their family relationship as well as problems or illnesses within the family. This information, often represented graphically as a family tree, facilitates analysis of inheritance patterns. Study of a trait or disease begins with the affected person (the index individual). The pedigree is drawn as the relatives are described. One begins with the siblings of the index individual and proceeds to the parents; relatives of the parents, including brothers, sisters, nephews, nieces, grandparents, and so on. At least three generations are usually included. Illnesses, hospitalisations, causes of death, miscarriages, abortions, congenital anomalies, and any other unusual features are recorded.
Premature coronary heart disease	For the purpose of this guideline, this refers to a coronary event that has occurred (1) before 55 years of age in a male index individual or 65 years of age in a female index individual, (2) before 60 years of age in a first-degree relative, or (3) before 50 years of age in a second-degree relative.
Proband	The affected (index) individual through whom a family with a genetic disorder is ascertained.
Second-degree relative	A person's biological grandparent, grandchild, uncle, aunt, niece, nephew, half sister or half brother.
Simon Broome register	A computerised research register of people with FH, based in Oxford. Research from this voluntary register has led to several publications describing the natural history of FH in the UK. The 'Simon Broome criteria' for diagnosis were based on a study of this group of people with FH.
Specialist	One who has expertise in a particular field of medicine by virtue of additional training and experience. For this guideline, we use specialist to refer to a healthcare professional with an expertise in FH.
Specialist centre	The definition of a specialist centre is not rigid and is based on a combination of patient treatment services, numbers and ages of people attending there, the presence of a multi-disciplinary team (which may include, for example, physicians, lipidologists, specialist nurses and dietitians), the ability to manage the more unusual manifestations of the condition and the additional functions such as research, education and standard setting. Care is supervised by expert healthcare professionals but shared with local hospitals and primary care teams. Although details of the model may vary between patients and areas, the key is that specialist supervision oversees local provision with the patient seen at diagnosis for initial assessment and then at least annually for review.
Tendon xanthomata	A clinically detectable nodularity and/or thickening of the tendons caused by infiltration with lipid-laden histiocytes (macrophages in connective tissue). A distinctive feature of FH that most frequently affects the Achilles tendons but can also involve tendons on the back of the hands, elbows and knees.
Third-degree relative	A person's biological great grandparent, great grandchild, great aunt, great uncle, first cousin, grand nephew or grand niece.
Urgent referral	For the purposes of this guideline, urgent referral is as soon as possible with a maximum of 14 days.

Appendix E: Diagnostic criteria

Simon Broome diagnostic criteria for index individuals (probands)¹⁰

Diagnose a person with **definite** familial hypercholesterolaemia (FH) if they have:

- cholesterol concentrations as defined in table 1 and tendon xanthomas, or evidence of these signs in first- or second-degree relative

or

- DNA-based evidence of an LDL-receptor mutation, familial defective apo B-100, or a PCSK9 mutation.

Diagnose a person with **possible** FH if they have cholesterol concentrations as defined in table 1 **and** at least one of the following.

- Family history of myocardial infarction: aged younger than 50 years in second-degree relative or aged younger than 60 years in first-degree relative.
- Family history of raised total cholesterol: greater than 7.5 mmol/l in adult first- or second-degree relative or greater than 6.7 mmol/l in child, brother or sister aged younger than 16 years.

Table 1 Cholesterol levels to be used as diagnostic criteria for the index individual¹

	Total cholesterol	LDL-C
Child/young person	> 6.7 mmol/l	> 4.0 mmol/l
Adult	> 7.5 mmol/l	> 4.9 mmol/l

¹ Levels either pre-treatment or highest on treatment.

LDL-C, low-density lipoprotein cholesterol.

¹⁰ Marks D, Thorogood M, Neil HA, Humphries SE (2003) A review on the diagnosis, natural history, and treatment of familial hypercholesterolaemia. *Atherosclerosis* 168 (1): 1–14.
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Gender- and age-specific LDL-C criteria for the diagnosis of FH in relatives of a person with FH

These gender- and age-specific LDL-C criteria are to be used for the diagnosis of FH in the relatives of an index case with FH where the family mutation has not been identified. These are intended for use by healthcare professionals with expertise in FH.



Relatives with LDL-C levels in the green zone are unlikely to have FH. In these instances, manage the person's coronary heart disease risk as in the general population (see 'Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease', NICE clinical guideline 67).



Relatives with LDL-C levels in the red zone are likely to have a clinical diagnosis of FH.



The diagnosis of FH for relatives in the grey zone is uncertain. A further measurement of LDL-C concentration should be carried out, and if the level is still in the grey zone this should be repeated annually. If the person's LDL-C concentration remains in the grey zone then coronary heart disease risk should be assessed and managed as in the general population (see 'Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease', NICE clinical guideline 67).

LDL-C females*

LDL-C females					
Age (years)					
0 to 14	15 to 24	25 to 34	35 to 44	45 to 54	55 and older
5.3	5.3	5.3	5.3	5.3	5.3
5.2	5.2	5.2	5.2	5.2	5.2
5.1	5.1	5.1	5.1	5.1	5.1
5.0	5.0	5.0	5.0	5.0	5.0
4.9	4.9	4.9	4.9	4.9	4.9
4.8	4.8	4.8	4.8	4.8	4.8
4.7	4.7	4.7	4.7	4.7	4.7
4.6	4.6	4.6	4.6	4.6	4.6
4.5	4.5	4.5	4.5	4.5	4.5
4.4	4.4	4.4	4.4	4.4	4.4
4.3	4.3	4.3	4.3	4.3	4.3
4.2	4.2	4.2	4.2	4.2	4.2
4.1	4.1	4.1	4.1	4.1	4.1
4.0	4.0	4.0	4.0	4.0	4.0
3.9	3.9	3.9	3.9	3.9	3.9
3.8	3.8	3.8	3.8	3.8	3.8
3.7	3.7	3.7	3.7	3.7	3.7
3.6	3.6	3.6	3.6	3.6	3.6
3.5	3.5	3.5	3.5	3.5	3.5
3.4	3.4	3.4	3.4	3.4	3.4
3.3	3.3	3.3	3.3	3.3	3.3
3.2	3.2	3.2	3.2	3.2	3.2

* From Starr B, Hadfield SG, Hutten BA, Landsberg P, Leren TP, Damgaard D, Neil HAW and Humphries SE (2008) Development of sensitive and specific age- and gender-specific low density lipoprotein cholesterol cutoffs for diagnosis of first-degree relatives with familial hypercholesterolaemia in cascade testing. *Clinical Chemistry and Laboratory Medicine* 46 (6): 791–803.

LDL-C males*

LDL-C males					
Age (years)					
0 to 14	15 to 24	25 to 34	35 to 44	45 to 54	55 and older
5.3	5.3	5.3	5.3	5.3	5.3
5.2	5.2	5.2	5.2	5.2	5.2
5.1	5.1	5.1	5.1	5.1	5.1
5.0	5.0	5.0	5.0	5.0	5.0
4.9	4.9	4.9	4.9	4.9	4.9
4.8	4.8	4.8	4.8	4.8	4.8
4.7	4.7	4.7	4.7	4.7	4.7
4.6	4.6	4.6	4.6	4.6	4.6
4.5	4.5	4.5	4.5	4.5	4.5
4.4	4.4	4.4	4.4	4.4	4.4
4.3	4.3	4.3	4.3	4.3	4.3
4.2	4.2	4.2	4.2	4.2	4.2
4.1	4.1	4.1	4.1	4.1	4.1
4.0	4.0	4.0	4.0	4.0	4.0
3.9	3.9	3.9	3.9	3.9	3.9
3.8	3.8	3.8	3.8	3.8	3.8
3.7	3.7	3.7	3.7	3.7	3.7
3.6	3.6	3.6	3.6	3.6	3.6
3.5	3.5	3.5	3.5	3.5	3.5
3.4	3.4	3.4	3.4	3.4	3.4
3.3	3.3	3.3	3.3	3.3	3.3
3.2	3.2	3.2	3.2	3.2	3.2
3.1	3.1	3.1	3.1	3.1	3.1
3.0	3.0	3.0	3.0	3.0	3.0

* From Starr B, Hadfield SG, Hutten BA, Landsberg P, Leren TP, Damgaard D, Neil HAW and Humphries SE (2008) Development of sensitive and specific age- and gender-specific low density lipoprotein cholesterol cutoffs for diagnosis of first-degree relatives with familial hypercholesterolaemia in cascade testing. *Clinical Chemistry and Laboratory Medicine* 46 (6): 791–803.