NICE National Institute for Health and Care Excellence

NICE Pathways

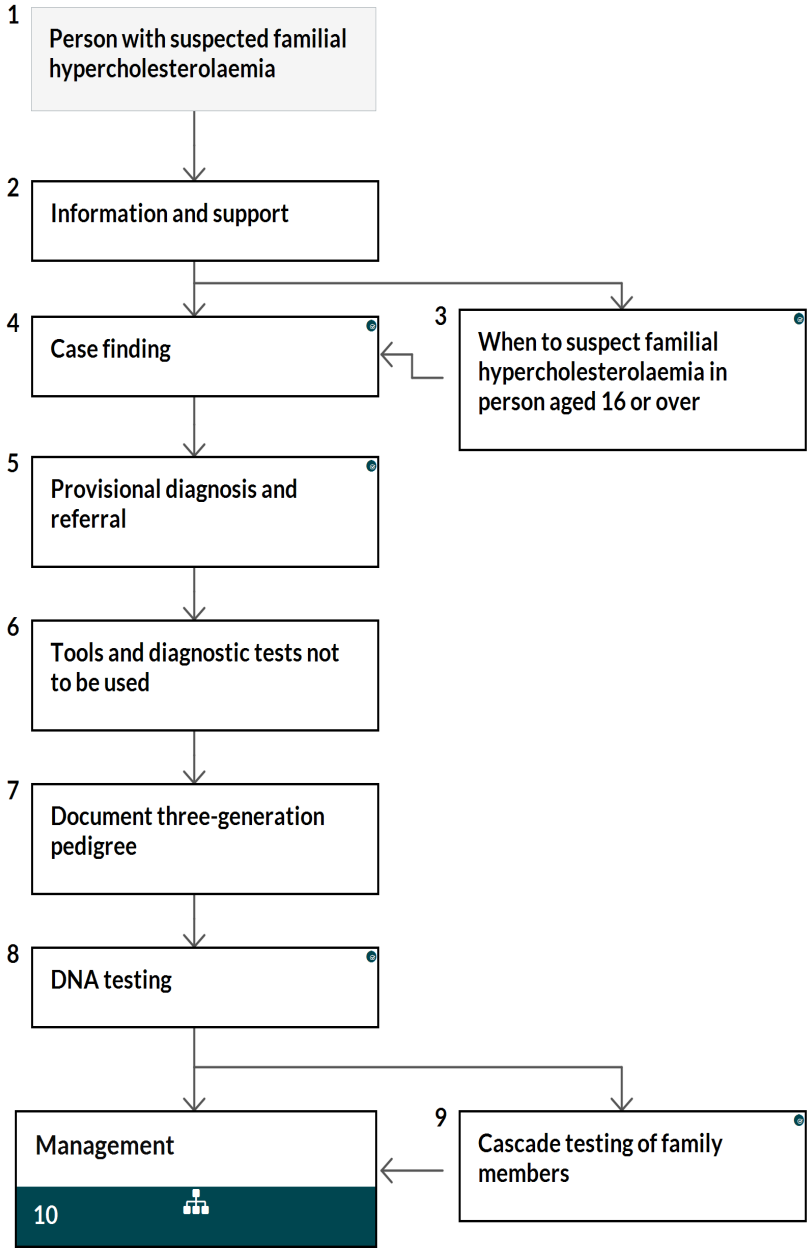
Familial hypercholesterolaemia: case finding and diagnosis

NICE Pathways bring together everything NICE says on a topic in an interactive flowchart. NICE Pathways are interactive and designed to be used online.

They are updated regularly as new NICE guidance is published. To view the latest version of this NICE Pathway see:

http://pathways.nice.org.uk/pathways/familial-hypercholesterolaemia
NICE Pathway last updated: 18 November 2020

This document contains a single flowchart and uses numbering to link the boxes to the associated recommendations.



1 Person with suspected familial hypercholesterolaemia

No additional information

2 Information and support

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.

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.

When considering cascade testing, a healthcare professional with expertise in FH should offer to facilitate the sharing of information about FH with family members.

Healthcare professionals should offer people with FH and their families written advice and information about patient support groups.

NICE has written information for the public on familial hypercholesterolaemia.

3 When to suspect familial hypercholesterolaemia in person aged 16 and over

Suspect FH as a possible diagnosis in adults with:

- a total cholesterol level greater than 7.5 mmol/l **or**
- a personal or family history of premature coronary heart disease (an event before 60 years in an index individual or first-degree relative).

Quality standards

The following quality statement is relevant to this part of the interactive flowchart.

1. Diagnosis

4 Case finding

Systematically search primary care records for people:

- younger than 30 years old, with a total cholesterol concentration greater than 7.5 mmol/l **and**
- 30 years or older, with a total cholesterol concentration greater than 9.0 mmol/l

as these are the people who are at highest risk of FH.

For people with a personal or family history of premature coronary heart disease (an event before 60 years in an index individual or first-degree relative), but whose total cholesterol is unknown, offer to measure their total cholesterol.

Quality standards

The following quality statement is relevant to this part of the interactive flowchart.

1. Diagnosis

5 Provisional diagnosis and referral

Healthcare professionals should exclude secondary causes of hypercholesterolaemia before a diagnosis of FH is considered.

Use the Simon Broome criteria or DLCN criteria [See page 8] to make a clinical diagnosis of FH in primary care settings. This should be done by a healthcare professional competent in using the criteria.

Refer the person to an FH specialist service for DNA testing if they meet the Simon Broome criteria for possible or definite FH, or they have a DLCN score greater than 5.

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.

Healthcare professionals should consider a clinical diagnosis of homozygous FH [See page 8] in people aged 16 and over with a LDL-C concentration greater than 13 mmol/l and in under 16s 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 [See page 9].

To confirm a diagnosis of FH, healthcare professionals should undertake two measurements of LDL-C concentration because biological and analytical variability occurs.

Child at risk of homozygous familial hypercholesterolaemia

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.

Referrals for under 16s

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.

Quality standards

The following quality statements are relevant to this part of the interactive flowchart.

1. Diagnosis
2. Specialist referral
3. DNA testing

6 Tools and diagnostic tests not to be used

Ultrasonography of the Achilles tendon is not recommended in the diagnosis of FH.

Coronary heart disease risk estimation tools, such as QRISK2 and 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 (an event before 60 years in an index individual or first-degree relative).

7 Document three-generation pedigree

When considering a diagnosis of FH, healthcare professionals with expertise in FH should use standardised pedigree [See page 8] terminology to document, when possible, at least a three-generation pedigree. This should include relatives' age of onset of coronary heart disease, lipid concentrations [See page 8] 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.

8 DNA testing

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.

Child at risk because of one affected parent

In children aged 0 to 10 years at risk of FH because of 1 affected parent, offer a DNA test at the earliest opportunity. If testing of a child at risk has not been undertaken by the age of 10 years, offer an additional opportunity for a DNA test.

Quality standards

The following quality statement is relevant to this part of the interactive flowchart.

4. Diagnosis in children under 10 years

9 Cascade testing of family members

Carry out cascade testing using DNA testing to identify affected first-degree relatives and second-degree relatives and, when possible, third-degree relatives of people with a genetic diagnosis of FH.

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.

Healthcare professionals with expertise in FH should explain what is meant by cascade testing,

and discuss its implications with all people with FH.

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

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 population (see the NICE Pathway on cardiovascular disease prevention).

Quality standards

The following quality statements are relevant to this part of the interactive flowchart.

2. Specialist referral

5. Cascade testing

10 Management

See Familial hypercholesterolaemia / Managing familial hypercholesterolaemia

Dutch Lipid Clinic Network (DLCN) criteria/score

A method of assessing whether a person has FH. It is based on personal and family medical history, clinical signs, LDL-C concentration and DNA testing. A score is attributed to each component; the higher the score, the higher the likelihood of the person having FH.

Homozygous familial hypercholesterolaemia

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.

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.

Lipid concentrations

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. Such tests are usually done in a clinical biochemistry laboratory.

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.

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, pharmacists 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.

Glossary

Cascade testing

(a mechanism for identifying people at risk of a genetic condition by a process of family tracing; for FH the test employed is a DNA test where a disease-causing mutation has been identified in the index individual)

Coronary heart disease

(an event is defined as angina, acute coronary syndrome, myocardial infarction, need for coronary artery bypass grafting, need for percutaneous coronary intervention or definite coronary artery disease on coronary angiography)

Family history

(the structure and relationships within the family that relates information about diseases in family members)

FH

familial hypercholesterolaemia

First-degree relative

(a person's biological parents, brothers and sisters, and children)

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(a person's biological parents, brothers and sisters, and children)

Index individual

(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; synonymous with proband)

LDL-C

low-density lipoprotein cholesterol

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)

Secondary causes of hypercholesterolaemia

(causes of hyperlipidaemia other than familial, including uncontrolled diabetes mellitus, obesity, excess alcohol consumption, untreated hypothyroidism and some medications, for example, thiazide diuretics and ciclosporin)

Second-degree relatives

(a person's biological grandparent, grandchild, uncle, aunt, niece, nephew, half sister or half brother)

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 relatives

(a person's biological great grandparent, great grandchild, great aunt, great uncle, first cousin,

grand nephew or grand niece)

Sources

Familial hypercholesterolaemia: identification and management (2008 updated 2019) NICE guideline CG71

Your responsibility

Guidelines

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

Local commissioners and providers of healthcare have a responsibility to enable the guideline to be applied when individual professionals and people using services wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with complying with those duties.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Technology appraisals

The recommendations in this interactive flowchart represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take these recommendations fully into account, alongside the

individual needs, preferences and values of their patients. The application of the recommendations in this interactive flowchart is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Commissioners and/or providers have a responsibility to provide the funding required to enable the recommendations to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Medical technologies guidance, diagnostics guidance and interventional procedures guidance

The recommendations in this interactive flowchart represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, healthcare professionals are expected to take these recommendations fully into account. However, the interactive flowchart 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.

Commissioners and/or providers have a responsibility to implement the recommendations, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity, and foster good relations. Nothing in this interactive flowchart should be interpreted in a way that would be inconsistent with compliance with those duties.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.