Familial hypercholesterolaemia (FH) Diagnostic criteria and investigations

Clinical presentation

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Identification of relatives followed by cholesterol cascade testing if appropriate

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Genotype negative - index case

Genotype requesting

Genotype negative - index case

Information for patients and carers

Information for patients and carers

Refer relative to local lipid clinic

Relative is FH positive for index case mutation

Relative is FH negative - FH excluded in terms of index case mutation

Relative is FH positive for index case mutation

FH negative for index mutation with low cholesterol

FH negative for index mutation with elevated cholesterol

Discharge from cascade programme

Continuing shared care

Continuing care

Paediatric-family lipid clinic

Adult lipid clinic

Primary care

Shared care

Refer relative to local lipid clinic

Offer genetic cascade testing to relatives (Family Cascade Programme via genetic counsellors)

Patient lifestyle education

Obtain family history/pedigree - FH clinical nurse specialist

Offer DNA testing - FH clinical nurse specialist and consultant

Genotype requesting and Consent forms

Genotype positive - index case

FH negative for index mutation with low cholesterol

FH negative for index mutation with elevated cholesterol

Adult lipid clinic

Paediatric-family lipid clinic

Continuing care

Shared care

Primary care

Refer relative to local lipid clinic

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1 Familial hypercholesterolemia (FH)

Quick info:

• Familial hypercholesterolemia (FH) is an autosomal dominant inherited metabolic disorder with a prevalence of around 1 in 500 in the UK similar to Type 1 diabetes. This equates to approximately 6000 cases of FH in Wales with a high blood cholesterol concentration. The condition is caused by an LDL-Receptor mutation (chromosome 19) familial defective Apo B-100 (chromosome 2) or a PCSK9 mutation (chromosome 1).

• The heterozygous form occurs with a gene frequency of 1 in 500 of the population making it one of the most common simply inherited disorders. The FH heterozygous individuals will have serum cholesterol of about 9-16 mmol/L, tendon xanthomata and a family history of hypercholesterolemia and premature heart disease. This is manifest from birth and contrasts with the polygenic form or common hypercholesterolemia, also inherited, which does not usually become manifest until adulthood.

• The homozygous form has an incidence of one in a million of the population. These individuals have a distinct syndrome characterised by severe hypercholesterolemia of 15-30 mmol/L, an unique form of cutaneous xanthomata and signs of coronary artery disease as early as 5 years of age ending typically in death from myocardial infarction (MI) by their early twenties.

References:


2 Information for patients and carers

Quick info:

Useful websites:

• British Heart Foundation
  • reducing blood cholesterol
  • eating well
  • stop smoking
• Heart UK
• NHS Direct Wales
• Smoking Helpline Wales 0800 1 690 169
• Stop Smoking Wales 0800 085 2219

3 Diagnostic criteria and investigations

Quick info:

Diagnostic criteria:

• A diagnosis of familial hypercholesterolemia (FH) should be considered in those patients who have raised total cholesterol concentrations (typically greater than 7.5 mmol/L), especially if there is a personal or family history of premature coronary heart disease.

• Secondary causes of hypercholesterolemia should be excluded and treated before considering a diagnosis of FH.

Investigations to include:

• creatinine, electrolytes and alanine aminotransferase (ALT), alkaline phosphatase (ALP), bilirubin, albumin, (aspartate aminotransferase (AST), gamma glutamyl transferase (GGT) if requested/indicated)
• thyroid stimulating hormone (TSH) and free T4
• fasting glucose (if abnormal, refer to 'Diabetes' pathway)
• creatine kinase
• fasting lipid profile (TG, cholesterol, HDL-Chol and LDL-Chol)

The National Institute for Health and Clinical Excellence (NICE) recommend use of the Simon Broome Criteria to make a diagnosis of familial hypercholesterolemia (FH).

Diagnose a person with potential FH if they have:
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- total cholesterol greater than 7.5mmol/L in an adult (>6.7 mmol/L in children under 16 years) or LDL cholesterol greater than 4.9 mmol/L (greater than 4.0 mmol/L in children under 16 years)

As definite FH if they also have:
- tendon xanthomata or evidence of these signs in first or second degree relative
- or DNA evidence of LDL-Receptor mutation, familial defective Apo B-100 or a PCSK9 mutation

or possible FH if they also have:
- 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 a child, brother or sister aged younger than 16 years)
- family history of myocardial infarction (aged younger than 50 years in second degree relative or aged younger than 60 years in first degree relative)

Absence of clinical signs (for example tendon xanthomata) does not exclude a diagnosis of FH

References:

4 Clinical presentation

Quick info:
To be checked by the general practitioner.

Xanthomata
- xanthomata (tendon xanthomata are diagnostic hallmarks of familial hypercholesterolaemia [FH])
- the most common sites for tendon xanthomata are in the tendons overlying the Achilles tendons and the knuckles
- less common sites include the extensor hallucis longus tendon and the triceps tendon
- they can also occur on the tibial tuberosity at the site of insertion of the patellar tendon (called a subperiosteal xanthomata)
- the skin overlying xanthomata is normal colour (ie. does not appear yellow)
- Achilles tendon xanthomata may become inflamed and patients may give a history of previous Achilles tenosynovitis
- xanthomata affecting the tendons in the dorsum of the hand are often fusiform or nodular (the hands should be examined with the fingers extended because they overlie the knuckles and may be missed when the fists are clenched)
- compare and palpate both sides for xanthomata. It is common to have bilateral xanthomata in definite FH patients but very rarely are they symmetrical. It is advisable to palpate both Achilles tendons simultaneously to compare sizes and discover subtle differences
- see images of tendon xanthomata (intranet)

Xanthelasma and corneal arcus:
- are not specific for FH (often occur earlier in life in patients with FH than in individuals with polygenic hypercholesterolaemia). If arcus seen in patients less than 45 years, consider FH
- many FH heterozygotes with obvious tendon xanthomata do not develop corneal arcus until later in life and may never develop xanthelasmas
- see images of xanthelasma and corneal arcus (intranet)

Ischaemic heart disease
- look for IHD in patient and whether there is family history of IHD

6 Clinical diagnosis of familial hypercholesterol- aemia NOT confirmed

Quick info:
Clinical examination, blood investigations to exclude secondary causes of hyperlipidaemia if not undertaken in primary care and ECG need to be undertaken within the Lipid clinic. Application of the Simon Broome criteria should be made to findings to decide whether a clinical diagnosis of FH can be made.
Familial hypercholesterolaemia and family cascade testing

If the patient does not now fulfil the required Simon Broome criteria for clinical diagnosis of familial hypercholesterolaemia but is hypercholesterolaemic, the patient still requires treatment of elevated cholesterol and lifestyle advice along with family members being made aware.

The relatives need to be aware of hypercholesterolaemia in the family and to gain access to investigation and treatment themselves if necessary. These patients should not go on to be genetically tested at this time as they do not fulfil the required criteria.

7 Clinical diagnosis of familial hypercholesterolaemia confirmed

Quick info:
Clinical examination, blood investigations to exclude secondary causes of hyperlipidaemia (if not already undertaken in primary care) and ECG need to be undertaken within the Lipid clinic. Application of the Simon Broome criteria should be made to findings to decide whether a clinical diagnosis of FH is able to be made. If confirmed then the Lipid clinic will treat the hypercholesterolaemia and base line investigations prior to the initiation of statin treatment.

The National Institute for Health and Clinical Excellence (NICE) recommend use of the Simon Broome Criteria to make a diagnosis of familial hypercholesterolaemia (FH).

Diagnose a person with potential FH if they have:

- total cholesterol greater than 7.5 mmol/L (>6.7 mmol/L in children under 16 years) or LDL cholesterol greater than 4.9 mmol/L (>4.0 mmol/L in children under 16 years)

As definite FH if they also have:

- tendon xanthomata or evidence of these signs in first or second degree relative
- or DNA evidence of LDL-Receptor mutation, familial defective Apo B-100 or a PCSK9 mutation

or possible FH if they also have:

- 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 a child, brother or sister aged younger than 16 years)
- family history of myocardial infarctions (aged younger than 50 years in second degree relative or aged younger than 60 years in first degree relative)

Absence of clinical signs (for example tendon xanthomata) does not exclude a diagnosis of FH

References:

8 Refer to FH clinical nurse specialist within the Region

Quick info:
Once clinical diagnosis of FH is confirmed request FH clinical nurse specialist to see the patient to give lifestyle advice and education, to discuss family history and draw family pedigree.

Explanation of genetic testing needs to be undertaken by FH nurse or consultant, the patient provided with information leaflet and the Genotype requesting form completed to determine whether the patient scores sufficient points by the Welsh-Dutch scoring system to qualify by current criteria for DNA testing (node 13)

9 Patient lifestyle education

Quick info:
Provide patients with advice and education on the following issues:

- specific level of risk of coronary heart disease
- diet:
  - advise patients to eat a cardioprotective diet, comprising:
    - fat intake 30% or less than total energy intake
    - saturated fat intake 10% or less of total energy intake – saturated fats should be replaced by monounsaturated and polyunsaturated fats
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• cholesterol intake less than 300mg/day
• five portions of fruit and vegetables per day
• two portions of fish per week, including a portion of oily fish
• minimise sugar and salt intake (less than 6g/day)

Dietary advice for all patients at high risk of cardiovascular disease (CVD) should be comprehensive and specific.
Encourage the patient to adhere to dietary recommendations which:
• modify lipid profile by lowering low density lipoprotein (LDL) cholesterol, lowering triglycerides and raising high density lipoprotein (HDL) cholesterol
• lower blood pressure (BP)
• control hypertension
• control diabetes mellitus

NB: If possible, consider involving a dietitian to monitor compliance with dietary recommendations and long-term follow-up of the patient’s dietary modifications and weight loss.

Useful websites:
British Heart Foundation and Heart UK

• physical activity:
  • 30 minutes of at least moderate intensity exercise a day at least 5 days a week (or maximum safe capacity for those unable to manage the recommended level)
• weight management:
  • the recommended body mass index (BMI) is between 20-25kg/m²
  • offer overweight and obese patients support and advice to achieve healthy weight
• alcohol consumption:
  • advise men to limit their alcohol intake to 3–4 units a day
  • advise women to limit their alcohol intake to 2–3 units a day
• smoking cessation:
  • advise patient to stop smoking (see ‘Smoking cessation’ pathway) and offer help with this

References:

10 Obtain family history/pedigree - FH clinical nurse specialist

Quick info:
FH clinical nurse specialist should obtain family history and pedigree along with information regarding age, mode of death of deceased relatives and if cholesterol levels are known. This information will be transferred onto PASS clinical software and utilised by genetic counsellors if genetic cascade testing takes place

11 Offer DNA testing - FH clinical nurse specialist and consultant

Quick info:
Offer a DNA test to patients with a clinical diagnosis of familial hypercholesterolaemia provided their Welsh-Dutch scoring demonstrates them eligible for DNA testing at this time. Provide the patient with information on the condition and the implications of DNA testing. Undertake patient audit questionnaire from all the information gathered so far. This document along with the Family History Form and pedigree to be filed in a family file.

Reference:

12 Genotype requesting
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Quick info:
The Welsh-Dutch scoring form is used to establish whether the patient is eligible for testing at the present time according to the agreed criteria. Obtain the patient's consent for testing and establish whether the patient is prepared to give consent to contact their relatives using their name as the proband with a mutation if positive or with a high cholesterol if mutation negative.

14 Genotype negative - index case

Quick info:
If the patient is genotype negative but is hypercholesterolaemic, the patient still requires treatment of elevated cholesterol and lifestyle advice along with family cascade testing using Cholesterol and LDL-Cholesterol as markers. The relatives need to be aware of hypercholesterolaemia in the family and to gain access to investigation and treatment themselves if indicated. This will either be a polygenic hypercholesterolaemia or as they have had so many indications suggesting FH they may have a mutation which is not yet able to be tested for. It is therefore important that these patients and their families have their hypercholesterolaemia treated and to remain on the PASS clinical database so that they may be revisited in a few years to see if their potential mutation has then been discovered. Whichever scenario prevails, these patients are also at an increased risk of coronary heart disease (CHD) and need to be treated. Inform GP of outcome of test.

15 Genotype positive - index case

Quick info:
• data gathered within the Lipid clinics on mutation positive index cases along with their pedigree and information on relatives is forwarded to the Database administrator who will populate the PASS clinical IT system with this information. The PASS clinical IT system combines pedigree drawing, data collection and workflow management along with despatching template letters and archiving of information
• template letters are automatically generated for direct contact with the relatives of index patients
• gain signed informed consent as to disclosure of the name of the index patient when contacting family members
• arrangements to be made via PASS clinical system for index case to be seen by the genetic counsellor
• inform GP of outcome of test including details of the specific mutation

References:
Rose D. Genetic disease patients may lose privacy rights to protect families. The Times 2009; September 26.

16 Identification of relatives followed by cholesterol cascade testing if appropriate

Quick info:
Relatives of patients where FH is not clinically confirmed need to be made aware of hypercholesterolaemia in the family and to gain access to investigation and treatment themselves if indicated. Relatives of genotype negative hypercholesterolaemic index cases will be subject to cholesterol cascade testing (see node 14)

17 Offer genetic cascade testing to relatives (Family Cascade Programme via genetic counsellors)

Quick info:
• ensure that all index patients who have an identified mutation of familial hypercholesterolaemia (FH) have been personally informed that they have an unequivocal diagnosis of FH
• offer appropriate counselling of proband of possible psychological, insurance and financial product implications
• if FH gene mutation has been identified use the mutation to identify affected relatives and not LDL cholesterol concentrations
• several members of each family, including children and women in their reproductive years will commonly require treatment and advice
• invite family members to attend for a session with genetic counsellor
• it is suggested that no more than 2 invitation letters are sent. If there is still no response from the relative, a concluding letter could be sent with a final reminder or a further invitation in 2-5 years
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- relatives outside Wales will also receive a letter advising them of the finding of a family mutation and recommending they visit their GP. A letter will also be sent to that relative's local genetic service for them to follow up that individual
- contact with the genetic counsellor will lead to arrangements of meetings to learn further pedigree, inform relatives about the nature of FH, the purpose of genotype testing and the undertaking of testing of the first, second and possibly third degree relatives for the index mutation
- Cholesterol and LDL-Cholesterol estimations will be undertaken at the same time and the results sent from the local laboratory to the Molecular Genetics Laboratory at University Hospital of Wales
- further interviews will take place with the relatives to convey the outcomes of the testing and the implications of the results

Reference:

18 Treat hyperlipidaemia

Quick info:
- the treatment of hypercholesterolaemia whether it be familial hypercholesterolaemia or not still needs to be addressed
- treatment may include:
  - statins
  - statins with ezetimibe
  - bile acid sequestrant
  - fibrate
  - nicotinic acid

References:

19 Relative is FH negative - FH excluded in terms of index case mutation

Quick info:
A letter from the genetic counsellor should be given to the patient and to the GP providing results of genetic testing and the cholesterol level.

References:

20 Relative is FH positive for index case mutation

Quick info:
A letter from the genetic counsellor should be given to the patient and to the GP providing the results of genetic testing and the cholesterol level.

NB: It is imperative that this relative who is genotype positive for an index mutation is referred to the Lipid clinic in their locality, is treated and continues to have some contact with the Lipid clinic as shared care with the GP, as and when required. Their families, not involved in the first cascade testing procedure will need to be contacted for genetic testing and the pathway followed again.

References:
21 Adult lipid clinic

Quick info:
Adult Lipid clinics and clinics with specialist lipid interest should be held in secondary care and led by the consultant and/or the FH clinical nurse specialist.

22 Paediatric-family lipid clinic

Quick info:
The referral should be to a specialist with expertise in FH in children and young people in an appropriate child/young person focussed setting. This will value the child's view and validate their voice in making decisions impacting on their lives. There should be a child focussed facility or space available.
The approximate clinic visits within secondary care would be at:
• diagnosis
• 3 months after beginning treatment
• 6 monthly follow up if well
• annual follow up thereafter until the age of 16-18 years if indicated
These clinics will be undertaken as combined clinics with the paediatrician and lipidiologist.
Reference:

23 FH negative for index mutation with low cholesterol

Quick info:
For relatives who are genotype negative with normal cholesterol levels further reference may be made to gender- and age-specific criteria for LDL-Cholesterol concentration measurements provided in tables 2 and 3 in NICE guidance. The LDL-Cholesterol concentrations should fall within the green area so that the relative may be reassured that no further action beyond adherence to a healthy lifestyle is required.
References:

24 FH negative for index mutation with elevated cholesterol

Quick info:
In relatives who are genotype negative for the family mutation but hypercholesterolaemic the GP should make further reference to gender- and age-specific criteria for LDL-Cholesterol concentration measurements provided in tables 2 and 3 in NICE guidance. If the LDL-Cholesterol concentrations fall outside the green area, a diagnosis of FH should be considered in spite of being negative for the index mutation. The patient then needs to be assessed by the GP as per the FH pathway criteria (nodes 2 and 3), excluding all secondary causes of hypercholesterolaemia. Referral to the Lipid clinic is advised if appropriate. If no other mutation for FH is found on genotype testing, these patients still need their hypercholesterolaemia treated and a database of these patients monitored. As methodologies improve and more mutations associated with FH and LDL Receptor defects are revealed, it may be appropriate to process these patients for genotype testing once again, eg. in 5 years time.
References:

25 Continuing care
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Quick info:
Continuing care for adults may be in primary care, secondary care or as shared care dependent upon the clinical condition of the patient.

- a structured review should be conducted at least once a year with baseline blood investigations undertaken along with, if indicated, an electrocardiogram and/or exercise ECG

26 Continuing shared care

Quick info:
- paediatric continuing shared care until 16-18 years of age, dependent upon the individual
- a structured review should be conducted at least once a year

Reference:

27 Primary care

Quick info:
- a structured review should be conducted at least once a year with baseline blood investigations undertaken along, if indicated, with an electrocardiogram and/or exercise ECG

Reference:

28 Shared care

Quick info:
- a structured review should be conducted at least once a year with baseline blood investigations undertaken along, if indicated, with an electrocardiogram and/or exercise ECG

Reference:

29 Discharge from cascade programme

Quick info:
A letter from the genetic counsellor should be given to the patient and GP giving results of genetic testing and cholesterol level and discharged from cascade programme.

References:

30 Refer relative to local lipid clinic

Quick info:
It is imperative that a relative who is genotype positive for an index mutation and a relative who is genotype negative for index mutation, but hypercholesterolaemic, be referred to the Lipid clinic in their locality, be treated and continue to have some contact with the Lipid clinic as shared care with the GP, as and when required.
The genotype negative hypercholesterolaemic relative needs to be assessed further according to the criteria of the pathway and may well need to be processed through the pathway as an index case requiring full genotype testing.
Familial hypercholesterolaemia and family cascade testing

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Evidence summary for Familial hypercholesterolaemia and family cascade testing

This pathway has been developed as part of the All Wales Familial Hypercholesterolaemia Cascade Testing Initiative supported by the Welsh Assembly Government and the British Heart Foundation. The development of the pathway was undertaken by a multidisciplinary group comprising representatives from across primary and secondary care in Wales, including GPs, Chemical Pathology Consultants, Metabolic and Integrated Medicine Consultants, Cardiology consultants, Genetic consultants and counsellors, specialist nurses and managers. It has been approved by the Cardiac Networks Steering Group for the FH Cascade Initiative and signed off by the NHS Wales Medical Executive Group. The pathway is consistent with quality appraised guidelines published as NICE clinical guideline 71, August 2008. All intervention nodes have been assessed for consistency with high quality guidelines and underlying evidence. The references are contained within relevant nodes.