Guidelines for the North, East and West (NEW) Yorkshire and Humber Familial Hypercholesterolaemia (FH) identification and cascade screening service

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Executive Summary

This document describes the proposed development within the North, East and West (NEW) Yorkshire and Humber involving the existing specialist lipid clinics, to provide a patient centred service for familial hypercholesterolaemia (FH) which would allow optimal compliance with the NICE guideline (CG71):" Identification and management of Familial Hypercholesterolaemia", published in August 2008. In 2015, the Yorkshire & the Humber Strategic Clincial Network successfully supported an application to British Heart Foundation for funding of four Familial Hyperchoesterolaemia (FH) nurses to develop a regional FH service across the North, East and West (NEW) Yorkshire and Humber region. The consortia bid was based on a lead provider (York Teaching Hospitals NHS Foundation Trust) and lead commissioner (NHS Vale of York CCG) model to cover 14 Clinical Commissioning Groups (CCGs). The dedicated FH identification and cascade screening service will involve a multidisciplinary approach which would identify majority of the undiagnosed FH patients within the region through specialist lipid clinics within 4 main Trusts including Calderdale, Hull, Leeds and York Hospitals. Primary care and cardiology services would refer patients with possible FH to the lipid clinics for assessment and entry into a care pathway for DNA diagnosis and family cascade testing, if the clinical diagnosis of FH is confirmed. Affected family members identified by cascade testing will be referred to a lipid clinic within the CCG wide network for assessment and initial management, with an ongoing management plan agreed with primary care.

Introduction

Heterozygous Familial Hypercholesterolaemia (FH) is an inherited lipid disorder and the most common genetic cause of premature coronary heart disease[1,2] (CHD) with an estimated population prevalence of 1 in 500 in the UK[3]. FH is an autosomal dominant disorder with a 50% chance of inheritance for the first degree relatives (parents, siblings and children). In FH individuals, concentrations of atherogenic LDL-cholesterol in the blood are typically doubled from birth leading to early development of advanced atherosclerosis with a 100 fold increased risk of CHD in the affected young patients[4]. Without treatment, affected men will frequently develop symptoms of coronary heart disease before 40 years and half will be symptomatic by the age of 50 years and affected women are symptomatic by 60 years of age.

FH is an underdiagnosed disorder with <15% of the affected patients being identified and treated in the UK[4,5]. FH accounts for 12% of all Myocardial Infarctions (MI) in patients under the age of 60[2]. The NICE FH Clinical Guideline- CG 71[6] was published in 2008 and recommends genetic testing of relatives of individuals known to have FH as the most cost effective strategy for early identification of affected individuals, leading to effective treatment through diet, lifestyle interventions and cholesterol lowering drugs with elimination of the excess coronary heart disease risk and premature mortality associated with FH.

Recommendations in the NICE CG71

The guideline contains key recommendations on the identification of patients with heterozygous FH and their relatives using cascade testing and their subsequent management which define the implementation strategy and are reflected in the audit standards:

- 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. [1.1.1]
- All individuals with FH should be referred to a specialist with expertise in FH for confirmation of diagnosis and initiation of cascade testing. [1.2.2]
- Cascade testing using a combination of lipid concentration measurement and DNA testing should be used to identify relatives of index cases with a clinical diagnosis of FH. [1.2.4]
- Children and young people diagnosed with, or being investigated for a diagnosis of, FH should be referred to a specialist with expertise in FH in an appropriate child focused setting. [1.3.1.14]
- All individuals and families with FH should be offered individualised nutritional advice from a healthcare professional with specific expertise in nutrition. [1.3.2.2]
- Prescription of a potent statin should usually be considered when trying to achieve a reduction of LDL-C concentrations of > 50% (from baseline). [1.3.1.2]
- All treated individuals with FH should have a regular structured review carried out at least annually. [1.5.1.1]

- The establishment and use of a nationwide family based follow-up system is recommended to enable comprehensive identification of affected individuals. [1.2.8]

Rationale for implementation of North, East and West (NEW) Yorkshire and Humber Familial Hypercholesterolaemia (FH) identification and cascade screening service

The dedicated FH identification and cascade screening service is implemented through established Specialist Lipid Clinics in the Yorkshire and Humber region based at 4 main Trusts including Calderdale, Hull, Leeds and York Hospitals. The total number of predicted patients with FH is approximately 6971 in the North, East and West (NEW) Yorkshire and Humber region. At present, the specialist lipid clinics are involved in the clinical assessment and management of patients with suspected FH. However, the diagnosis is unnecessarily delayed for other affected family members due to the lack of provision of cascade screening service. With the implementation of the dedicated FH service, patients will be evaluated for suitability of entry into the FH cascade testing pathway, genotyped, cascade testing undertaken for affected families and annual structured review offered to patients with FH. A cost-effective specialist clinical nurse led service can provide consistent cascade screening of all Index cases and add to the skill mix within a multidisciplinary team in the delivery of chronic disease care. Great Ormond street Hospital (GOSH) Genetics Service will undertake the DNA testing of all patients entered into the FH cascade testing pathway.

The proposed FH identification and cascade screening service will provide a means of achieving equity of service provision across the Yorkshire and Humber region with downstream savings on long term acute and primary care costs for a patient following a CVD event and the cost of revascularisation procedures. [1]. A dedicated FH identification and cascade screening service in the North, East and West (NEW) Yorkshire and Humber region will enable implementing and supporting the NICE guideline in the care of this specific group of patients together with being in line with the national public health strategy.

Scope of the guideline

This Guideline is designed for implementation of North, East and West (NEW) Yorkshire and Humber Familial Hypercholesterolaemia (FH) identification and cascade screening service to guide the BHF FH Clinical Nurse Specialist (CNS). The guideline also applies to all HCP's involved in the management (pathway of care) of FH patients and their families.

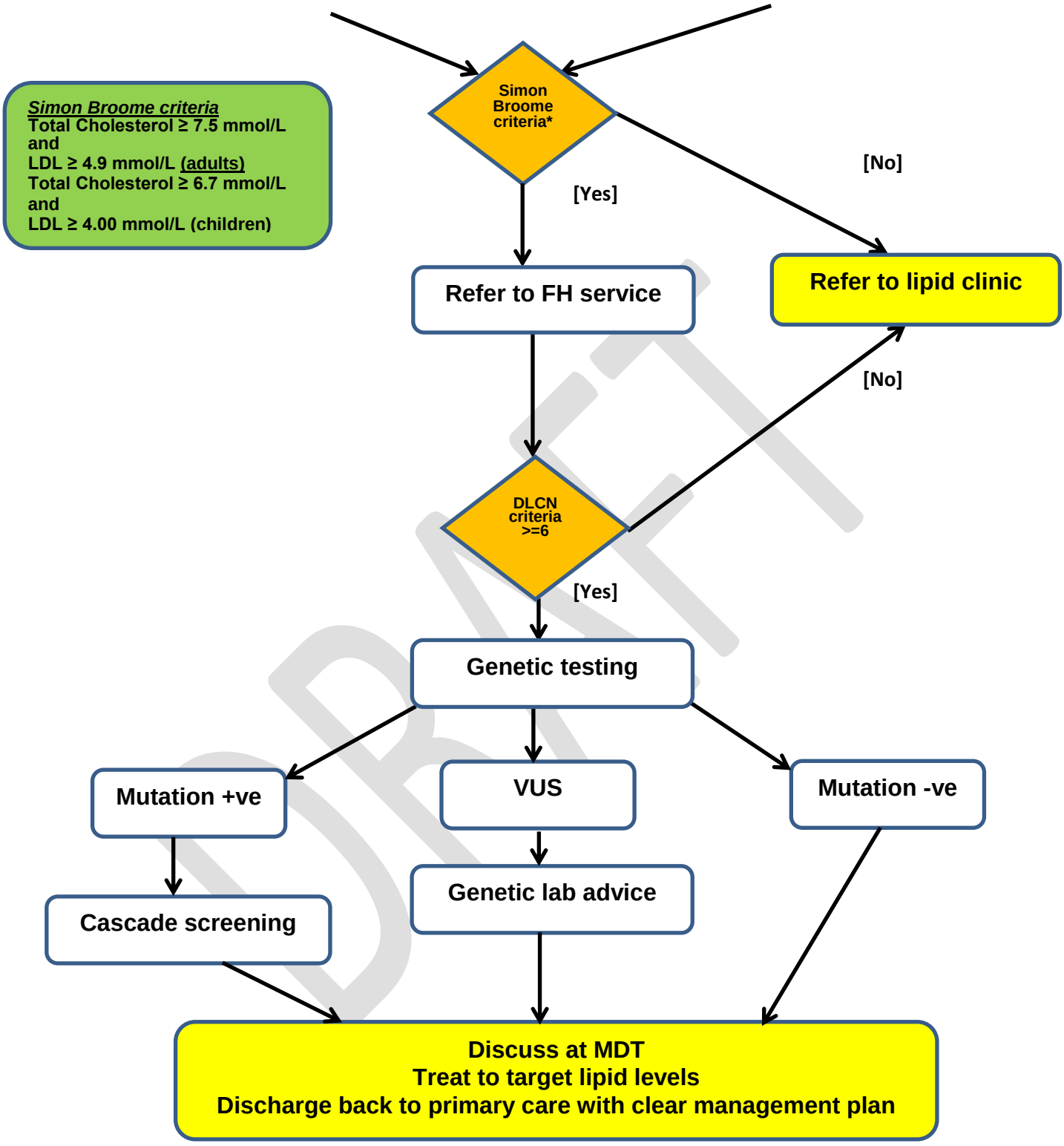
This Guideline aims to standardise the following in the North, East and West (NEW) Yorkshire and Humber region:

- The identification of individuals with FH
- The referral process for entry into entry into the FH cascade testing pathway
- Management of cascade screening for FH Index patients and their families, ensuring care is provided in appropriate settings for adults, children and young people.

- Annual structured review of patients with FH.
- Provision of accurate audit trail of data entered on the FH cascade testing pathway (via PASS).

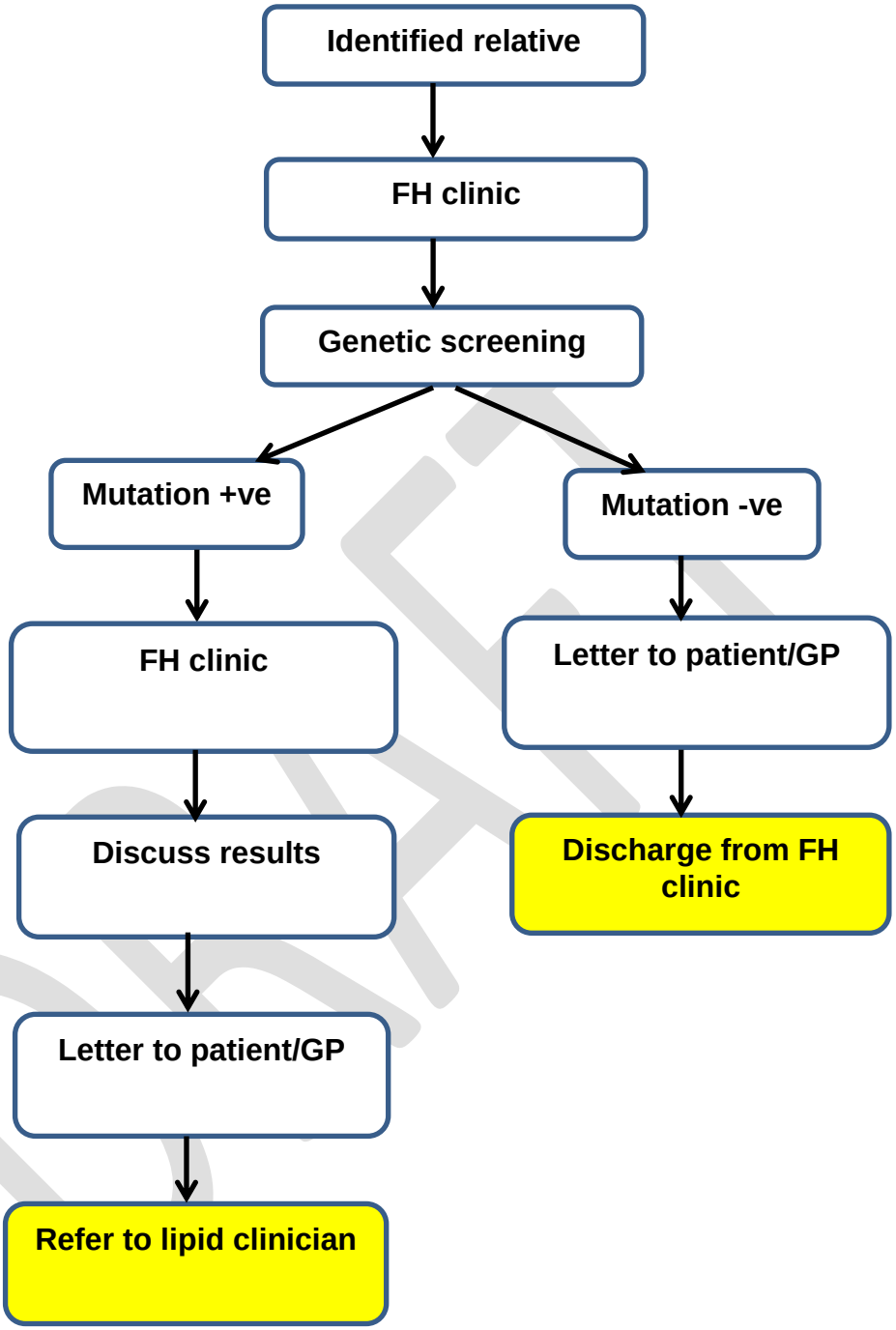
This SOP will outline the procedures agreed for the management of index patients with Familial Hypercholesterolaemia and cascade screening family members within the North, East and West Yorkshire & Humber (NEW Y&H) region. This SOP applies to all patients with Heterozygous FH (Adults). This document covers the FH Specialist Nurse 'standard operating procedures' (SOPs) for Index cases. This describes a pre-determined set of work instructions to ensure consistent processes are followed throughout and that patients receive appropriate care and are given adequate information to prepare them for cascade screening of their family and management of Familial Hypercholesterolaemia.

FH Index patient Pathway

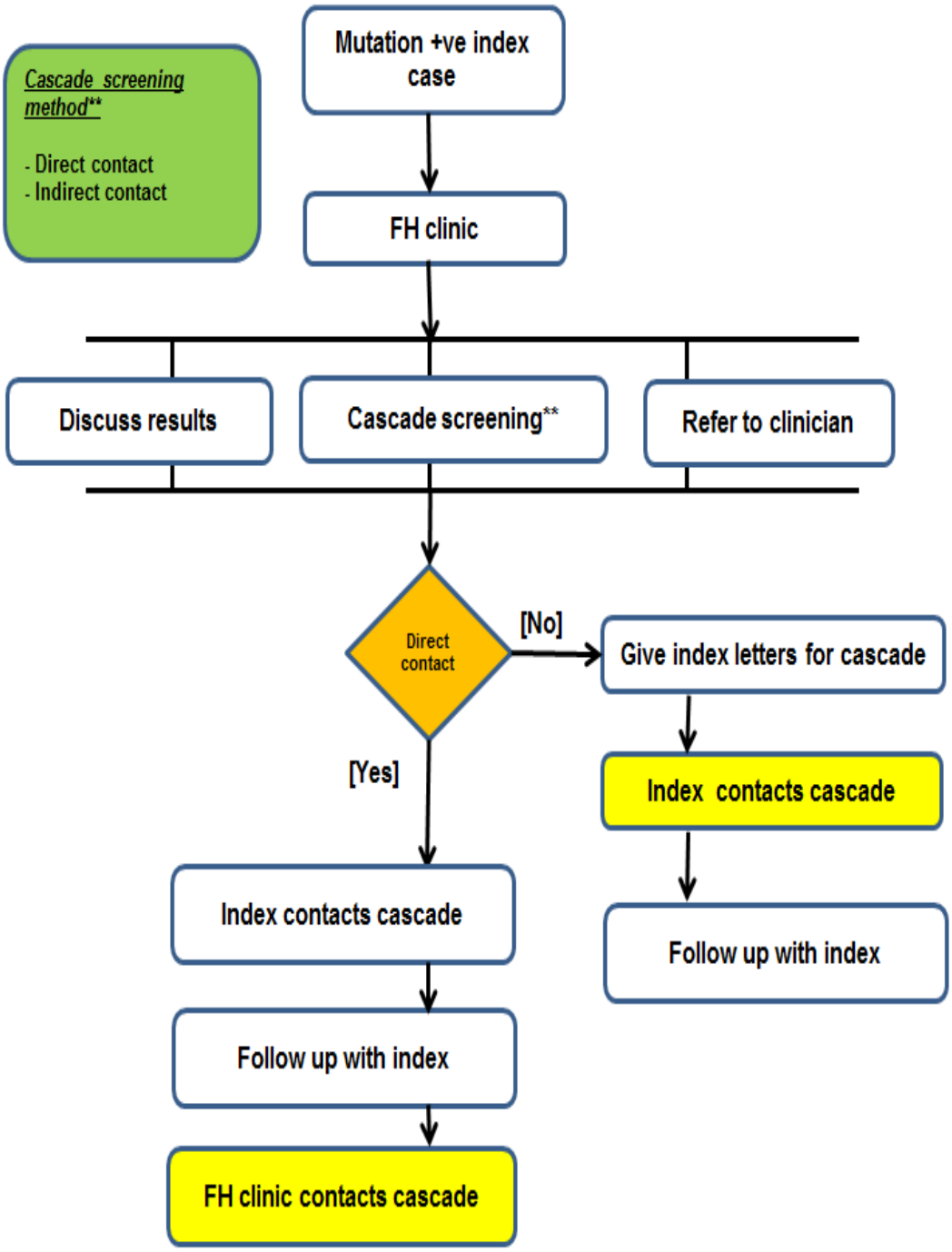


Simon Broome criteria
Total Cholesterol ≥ 7.5 mmol/L and LDL ≥ 4.9 mmol/L (adults)
Total Cholesterol ≥ 6.7 mmol/L and LDL ≥ 4.00 mmol/L (children)

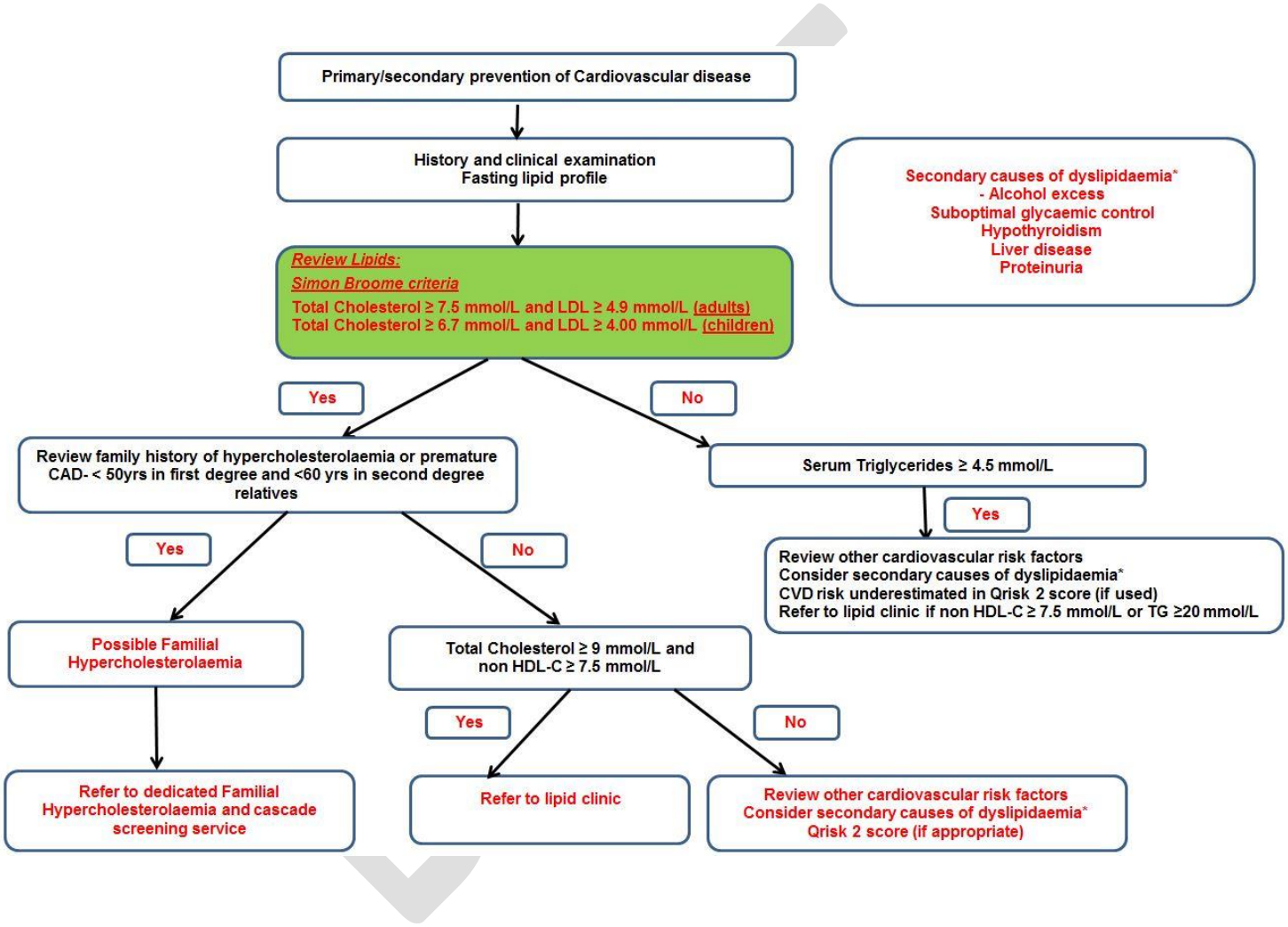
Cascade pathway



Direct and indirect contact for cascade screening



Primary care pathway



Details of FH Cascade Screening Pathway

1. Referrals in to lipid clinics from Primary or Secondary care: Assessment using Simon Broome Criteria and clinical examination[6].

    - Bloods tests including: Total Cholesterol, Triglycerides (TG), High Density lipoprotein (HDL) and Low Density lipoprotein (LDL). Renal panel (U&E'S), Fasting glucose or HbA1c, Liver function tests (LFT'S) and Thyroid function tests (TFT's) to exclude secondary causes of high cholesterol.

2. Lipid Clinics: Possible or definite Familial Hypercholesterolaemia (FH). Assessment using Simon Broome Criteria and clinical examination.

    - 2nd set of bloods for Cholesterol, TG and HDL, Lp (a) and genetic testing. Bloods (U&E's, Fasting glucose or HbA1c, LFT's, TFT's) to rule out secondary causes of high cholesterol, if not already done in primary care, urine dipstick test for protein and an ECG performed if not already done.

3. Once clinical diagnosis of FH is confirmed refer to FH Clinical Nurse Specialist (CNS) clinic for "Index case" appointment. FH nurse to send "Invitation to Index case appointment" letter to Index patient.

    - 1st Reminder letter to be sent at 4 weeks if no response from Index patient, 2nd reminder to be sent at 3 months.
    - Ensure that all index patients who have an identified FH mutation have been personally informed that they have an unequivocal diagnosis of FH (via lipid clinic appointment).

4. Index case Appointment: FH Nurse to explain condition and offer written FH information (if not already done in lipid clinic appointment) and recommend websites such as British Heart Foundation (BHF) or Heart UK for further reading by patient if they wish.

    - Offer appropriate counselling and support to Index case for possible psychological, insurance and financial product implications.
    - FH Nurse to give education & lifestyle advice to the patient on the following:
    - Information on specific level of risk of coronary heart disease: FH condition is considered high risk, due to the lifelong exposure from birth, to high levels of LDL cholesterol that cause accelerated atherosclerosis.

    Diet:

    Dietary advice for all patients at high risk of cardiovascular disease (CVD) should be comprehensive and specific[6]. Offer written information (HEART UK diet guide leaflet*,* regarding healthy eating and where possible referral to Dietician for specific patient centred advice. Use resources such as BHF, Heart UK and NHS Choices, Live Well websites.

    Advice patients to eat a cardioprotective diet[9] comprising:

    - Fat intake 30% or less than total energy intake
    - Saturated fat intake 7% or less of total energy intake – saturated fats should be replaced by monounsaturated and polyunsaturated fats.
    - 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)

- Eat at least 4 to 5 portions of unsalted nuts, seeds and legumes per week
- 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
- Discuss alcohol consumption: advice men and women to limit their alcohol intake to 2–3 units a day.

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) or total of 150 minutes /week.

Smoking:

- Advise patient to quit smoking and offer help with this (referral to smoking cessation service)[6,9].

FH nurse to explain process of cascade screening and reasons for this[7].

- FH nurse discusses and documents consent for cascade/segregation testing and direct contact of relatives by FH Nurse, in conjunction with Index case pre- informing family members that they will receive invitation letters for cascade screening.
- Direct contact the preferred method, as shown to be more effective at capturing relatives of index, unless Index patient specifically requests indirect contact[10].

FH nurse takes detailed family history and draws family pedigree along with information regarding age, cause of death of deceased relatives, cholesterol levels if known, if on any treatment (statins) and any known history of IHD of first, second and if possible third degree relatives[6,7].

- Information on relatives who may be at risk is documented on the family testing form (appendix) including names, dates of birth, and contact choices.
- This information will be completed with the addresses of relatives by the index patient and returned to the FH nurse via a Freepost stamped addressed envelope.
- Consent must be signed on the back of the family screening form, by the patient and FH Nurse, to allow for appropriate contact and documentation of above on PASS database.
- FH nurse to transfer this information onto the PASS clinical software database.

The PASS clinical IT system combines pedigree drawing, data collection and multidisciplinary (MDT) workflow management along with despatching template letters and archiving of information. PASS allows for a family number to be assigned that identifies and links individuals within a family.

- Patients will be informed their information from the pedigrees will be held on a secure national registry (PASS Database) and that this is not a DNA database, but used with their permission to facilitate cascade screening of their family members at risk of FH and to offer them testing no matter where they may live nationally.
- Use of a nationwide family based follow up system such as PASS allows for referral in to other lipid clinics out of area, for relatives not living locally, ensuring comprehensive identification of people affected with FH as recommended in NICE guidelines[6,9].
- Continuing care for Index case adults may be in primary, secondary care or as shared care in the long term, dependent upon the clinical condition of the patient, as reviewed by the lipid clinic

Consultant. This should include an annual structured review with baseline blood investigations undertaken along with, if indicated, an electrocardiogram and/or exercise ECG[6,9].

5. Template letters are generated from PASS by the FH nurse for direct contact with the relatives of index patients or for indirect contact if this method is preferred by the Index case[8,10].

   Direct contact- Addresses are required for letters to be sent out to individual relatives, letters to be sent on receipt of family form from Index case with relatives contact details (Appendix).

   Indirect contact- Family contact will be made using "Invitation to cascade screening" letters, sent to the index to hand deliver to family members (Appendix).

   - Obtain signed informed consent as to disclosure of the name of the index patient when contacting family members.
   - Write to the patient following the appointment to reiterate information given at the appointment.
   - Copy letter to Consultant to communicate invitation to relative to participate in the FH cascade screening service for adults. Copies of these letters to be filed in the patient notes.
   - Several members of each family, including women in their reproductive years will commonly require treatment and advice.
   - FH Nurse will book adult cascade relatives in to CNS clinic, who respond and agree to come in for screening.

6. 2nd attempt at direct contact of relatives by FH Nurse via template letters generated from the PASS clinical IT system after 12 weeks without reply from relatives.

   - If no reply on 2nd attempt to follow up, a 3rd and final attempt will be made 3 months later (to be input in to PASS timeframes).
   - FH Nurse will book adult cascade relatives in to CNS clinic, who respond and agree to come in for screening.

7. FH nurse sees relative of Index for cascade screening appointment.

   - FH nurse explains FH condition and therefore reason for cascade screening, implications of genetic testing and discusses lifestyle and cardio protective diet, physical activity and smoking, as above for Index case, with relative.

8. FH nurse explains targeted genetic testing and obtains informed consent for genetic test, consent for Cholesterol, HDL and TG blood samples and entry of their details on to the PASS FH registry.

   - Consent for genetic testing to be documented on the NEW Yorkshire and Humber genetics blood form.
   - FH nurse informs relative of likely timeframes for test results and process of notification of results.

9. Further information gathered about Relative and Relative's family regarding history of IHD, ages and treatment for cardiovascular disease (CVD).

10. FH Nurse follows up genetic test results in PASS database and cholesterol results.

11. Negative for Index mutation and low/normal cholesterol (Green on PASS system).

- 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 of the NICE clinical guideline 71 and patients can be discharged.
- 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[6].

12. Results letter sent to Relative by FH nurse, copies to GP and consultant (PASS templates). Relative may be discharged from cascade pathway.

13. Negative for Index mutation/ VUS but high cholesterol (Red on NICE risk stratification tables)
    - In relatives who are genotype negative for the family mutation but hypercholesterolaemic further reference should be made to the gender- and age-specific criteria for LDL-Cholesterol concentration measurements provided in tables 2 and 3 in NICE guidance for risk stratification and requires consultant review.

14. Results letter sent to Relative by FH Nurse, copies to GP and consultant providing the results of genetic testing and the cholesterol level (PASS templates).
    - Relative to be referred in to lipid clinic for further assessment* and review as new patient, excluding all secondary causes of hypercholesterolaemia.
    - If the family mutation for FH/VUS is not found on genotype testing, these patients will still need their hypercholesterolaemia treated and the need to adhere to a healthy lifestyle reinforced.
    - A structured review should be conducted at least once a year with baseline blood investigations undertaken along with, if indicated, an electrocardiogram. Continuing care can be in primary, secondary care or as shared care dependent upon the clinical condition of the patient (NICE 2008, NICE 2013).

15. Positive for Index mutation- provides unequivocal Diagnosis of FH. VUS presence requires consultant and MDT review.

16. Results letter sent to relative by FH nurse, copies to GP and Consultant, providing the results of genetic testing, the cholesterol level and referral to lipid clinic made for a “new patient” appointment (PASS templates).
    - It is imperative that this relative who is genotype positive for an index mutation is referred to the Lipid clinic in their locality as a new patient, is treated and continues to have some contact with the Lipid clinic as shared care with the GP (at least annual reviews) to monitor treatment, LDL C concentration (or non HDL*)* and for the possible development of signs and symptoms of CHD and to optimise management[6,9].
    - Their family members, not previously involved in the first cascade testing pathway, will then need to be contacted for genetic testing and the pathway followed again.
    - Annual review also allows progress of cascade testing of relatives to be monitored.

7. SOP

a. FH Index patient SOP

- FH nurse posts the **Appendix 7.1 "Index Invite letter to make appointment"** to contact patient. Letter is copied to patient notes, Lipid/Cardiology Consultant.
- The **Appendix 6 "FH appointment what to expect"** document is posted with the clinic appointment letter. This prompts the index patient to bring medical details of immediate family, names, dates of birth, contact details (address) and any cardiac/cholesterol related history. It also has details of the BHF and Heart UK website for information on Familial Hypercholesterolaemia.
- The index patient is prompted to contact the nurse within 2 weeks of date of original letter. If the patient has not contacted the service within 4 weeks of date of letter the FH nurse sends a 1st reminder using the **Appendix 7.2 "Index Invite letter first reminder".** Letter copied to patient notes and Lipid/Cardiology Consultant.
- If the patient has not contacted the service within 3 months of date of original letter the FH nurse 2nd sends a reminder using the **Appendix 7.3** "**Index Invite letter final reminder".** Letter copied to patient notes and Lipid/Cardiology Consultant.
- When the patient rings to book an appointment please checks 3 unique identifiers (i.e. forename/surname, DOB, NHS number). **Please also check the patients current GP as we need to match this against the CCG code and also add this to the central tracker for genetic tests hosted on the YTHFT X drive.**
- Once the patient rings to book an appointment send a copy of the standard outpatient letter to confirm appointment and hospital map/clinic location. Please adhere to local Trust policy.
- Please adhere to local Trust policy for DNA and cancellations.
- Upon arrival in clinic patient is booked into clinic by reception and demographics are checked.
- FH nurse checks for previous bloods on the system, recording baseline and target levels.
- FH nurse greets patient and ascertains if patient understands reason for referral, explains reason for appointment.
- Patient's cholesterol history/ lipid levels discussed.
- Patient's cholesterol/lipid treatments noted.
- FH nurse takes a detailed medical, social and family history: to include any symptoms of IHD, lifestyle risk factors (diet, alcohol and smoking), medication history.

- Educate about lifestyle, weight loss, activity, diet and smoking. Discuss areas for lifestyle improvements. Referral(s) made to clinic dietician, weight management and/ or smoking cessation as appropriate.
- FH nurse gives patient the "**BHF booklet"** about FH.
- FH nurse explains condition of FH and inheritance pattern. Refer to BHF resource **"Quick_guide_to_familial_hypercholesterolaemia"** Page 4 for guidance.
- FH nurse discusses heart attacks/artery, good/bad cholesterol, link with HDL and smoking, liver and LDL receptors, chromosome genes, pedigree, 50% chance of inheritance. Refer to BHF resource "**Life-with-familial-hypercholesterolaemia"** for guidance.
- FH nurse assesses patient for any phenotypic features of FH (Xanthomata, xanthelasma, corneal arcus). Refer to BHF resource **"Quick_guide_to_familial_hypercholesterolaemia"** Page 6 for guidance.
- Discusses any recent blood test results with patient.
- FH completes the "**PASS audit form"** in clinic as this can data be then input into PASS database later.
- Draws pedigree of Index case relatives (1st, 2nd and 3rd degree relatives) on the "**PASS audit form"**.
- Documents history of relatives on pedigree, medical history (specifically Cardiovascular, Diabetes, high blood pressure), drug history (statins), ages, alive or dead and causes of death where known.
- FH nurse discusses genetic testing. Implications and benefits to testing explained. Discusses three known genetic mutations. Refer to BHF resource "**Life-with-familial-hypercholesterolaemia"** page 13 for guidance.
- Dutch Lipid Clinical Network score calculated using the **Appendix 1**. If the genotype score is 6 or over, the patient is referred for genetic testing. If the genotypes score less than 6, index case is not referred for genetic testing but is referred back to the lipid clinic for management. Refer to **FH Index patient pathway** for guidance.
- If the genotype score is 6 or over the FH nurse gains and documents consent for genetic testing using the **Appendix 3** "**Genetic testing for Familial Hypercholesterolaemia consent form"**.
- FH nurse explains process and approximate timeframes of receiving results of genetic test. 8 weeks for a full mutation screen in an index case (next generation sequencing and MLPA).
- FH nurse explains the type of genetic testing reports and implications on cascade testing ie positive mutation, negative mutation, Variant of Unknown Significance (VUS).

- Blood samples taken for cholesterol and genetic testing by FH nurse.
- Blood samples for genetic testing need to be send to Great Ormond Street Hospital (GOSH) labs for testing as they are the provider. Refer to **"Genetic testing for FH service SOP".**
- Blood samples for FH testing should be in EDTA 5mls. Please refer to **Appendix 4** "**Joint genetic request form (GOSH)"** and **Appendix 5** "**service document (GOSH)"** for guidance on sample requirement.
- Please refer to **Appendix 4** "**Joint genetic request form (GOSH)"** for guidance on completing request forms and labels.
- Copy of consent form is not required by GOSH labs – it is presumed that consent has been obtained from patient prior to taking sample.
- EDTA tubes are not provided by GOSH labs; to be procured locally – please refer to **Appendix 4** "**Joint genetic request form (GOSH)"** for guidance on tube specifications.
- GOSH labs will invoice York Teaching Hospital NHS Trust (YTHFT) for the genetic tests. It is important to add correct referring clinician and contact details so that GOSH can match referral form and invoice accordingly. **Appendix 10 "Standard invoicing letter"** needs to accompany each **Joint genetic request form.**
- Please make clear on the **Joint genetic request form** and the **Standard invoicing letter** that this is an index case testing request.
- Clinic letter dictated using the **PASS template "Clinic letter to Patient after Index case appointment, copied to & Lipid Consultant via PASS Template"**.
- FH nurse updates PASS system as per "**PASS SOP"**.
- Local Trust templates to be used for Confirmation of new clinic appointment, cancellation and re-book appointment letter DNA (Did Not Attend) letters.

When patients are referred for genetic testing please update the central tracker hosted on the YTHFT X drive.

b. Cascade testing SOP

This SOP will outline the procedures agreed for the management of cascade screening of family members of index patients within the North, East and West Yorkshire & Humber (NEW Y&H) region. This SOP applies to all patients with Heterozygous FH (Adults). This describes a pre-determined set of work instructions to ensure consistent processes are followed throughout and that patients receive appropriate care and are given adequate information to prepare them for cascade screening for the management of Familial Hypercholesterolaemia.

CASCADE INVITE TO CLINIC

1 FH nurse posts the **Appendix 8.2 "Direct contact letter to invite for cascade screening/segregation testing appointment"** to contact patient.

2 The **Appendix "FH appointment what to expect"** document is posted with the clinic appointment letter. This prompts the index patient to bring medical details of immediate family, names, dates of birth, contact details (address) and any cardiac/cholesterol related history. It also has details of the BHF and Heart UK website for information on Familial Hypercholesterolaemia.

3 The index patient is prompted to contact the nurse within 2 weeks of date of original letter. If the patient has not contacted the service within 4 weeks of date of letter the FH nurse sends a 1st reminder using the **Appendix 8.3 "Cascade Invite letter to make appointment first reminder".**

4 If the patient has not contacted the service within 3 months of date of original letter the FH nurse 2nd sends a reminder using the **Appendix 8.4** "**Cascade Invite letter to make appointment final reminder".**

5 When the patient rings to book an appointment please checks 3 unique identifiers (i.e. forename/surname, DOB, NHS number). **Please also check the patients current GP as we need to match this against the CCG name/code and also add this to the central tracker for genetic tests hosted on the YTHFT X drive.**

6 Once the patient rings to book an appointment send a copy of the standard outpatient letter to confirm appointment and hospital map/clinic location. Please adhere to local Trust policy.

7 Please adhere to local Trust policy for DNA and cancellations.

8 Upon arrival in clinic patient is booked into clinic by reception and demographics are checked.

9 Review previous blood tests on the system, recording baseline and target levels.

10 FH nurse greets patient and ascertains if patient understands reason for referral, explains reason for appointment.

11 FH nurse takes a detailed medical, social, family and medication history: to include any symptoms of IHD, lifestyle risk factors (diet, alcohol and smoking), medication history.

12 Educate about lifestyle, weight loss, activity, diet and smoking. Discuss areas for lifestyle improvements. Referral(s) made to clinic dietician, weight management and/ or smoking cessation as appropriate.

13 FH nurse gives patient the "**BHF booklet"** about FH.

14 FH nurse explains condition of FH and inheritance pattern. Refer to BHF resource **"Quick_guide_to_familial_hypercholesterolaemia"** Page 4 for guidance.

15 FH nurse discusses heart attacks/artery, good/bad cholesterol, link with HDL and smoking, liver and LDL receptors, chromosome genes, pedigree, 50% chance of inheritance. Refer to BHF resource "**Life-with-familial-hypercholesterolaemia"** for guidance.

16 FH nurse assesses patient for any phenotypic features of FH (Xanthomata, xanthelasma, corneal arcus). Refer to BHF resource **"Quick_guide_to_familial_hypercholesterolaemia"** Page 6 for guidance.

17 Discusses any recent blood test results with patient.

18 FH completes the "**PASS audit form"** in clinic as this can data is then input into PASS database later.

19 FH nurse checks pedigree information with the cascade case. If the index case has not given consent to sharing their pedigree information this cannot be shared with the cascade case.

20 FH nurse checks history of relatives on pedigree, medical history (specifically Cardiovascular, Diabetes, high blood pressure), drug history (statins), ages, alive or dead and causes of death where known.

21 FH nurse discusses genetic testing. Implications and benefits to testing explained. Discusses the known genetic mutation that has been identified in index case. Refer to BHF resource "**Life-with-familial-hypercholesterolaemia"** page 13 for guidance. If the index case has not given consent to them being named this cannot be shared with the cascade case.

22 The FH nurse gains and documents consent for genetic testing using the "**Genetic testing for Familial Hypercholesterolaemia consent form"**.

23 FH nurse explains process and approximate timeframes of receiving results of genetic test (2 weeks for family mutation testing).

24 FH nurse explains the type of genetic testing reports and implications on cascade testing ie positive mutation and negative mutation.

25 Blood samples taken for cholesterol and genetic testing by FH nurse.

26 Blood samples for genetic testing need to be send to Great Ormond Street Hospital (GOSH) labs for testing as they are the provider. Refer to **"Genetic testing for FH service" SOP.**

27 Blood samples for FH testing should be in EDTA 5mls. Please refer to **Appendix 4 Joint genetic request form (GOSH)** and **Appendix 5 service document (GOSH)** for guidance on sample requirement.

28 Please refer to **Joint genetic request form (GOSH)** for guidance on completing request forms and labels.

29 Copy of consent form is not required by GOSH labs – it is presumed that consent has been obtained from patient prior to taking sample.

30 EDTA tubes are not provided by GOSH labs; to be procured locally – please refer to **joint genetic request form (GOSH)** for guidance on tube specifications.

31 GOSH labs will invoice York Teaching Hospital NHS Trust (YTHFT) for the genetic tests. It is important to add correct referring clinician and contact details so that GOSH can match referral form and invoice accordingly. **Appendix 10 Standard invoicing letter** needs to accompany each **Joint genetic request form.**

32 Please make clear on the **Joint genetic request form** and the **Standard invoicing letter** that this is a cascade screening request.

33 Clinic letter dictated using the **Appendix 9.1 "Clinic letter to Patient (both Index and cascade) copied to Lipid Consultant via PASS Template"**

34 Letter copied to patient notes and Lipid Consultant.

35 FH nurse updates PASS system as per "**PASS SOP"**.

36 **When patients are referred for genetic testing please update the central tracker hosted on the YTHFT X drive.**

c. Genetic test report SOP

Genetic test reports are received from GOSH labs via the following routes.

- Referring clinicians are sent a paper copy of the reports. Refer to **"Contact details"** for list of referring clinicians.
- Genetic reports can be accessed via the **nQuire Portal** using generic logins.

Positive mutations genetic test reports

- Positive mutations are reviewed along with clinical leads prior to contacting patients to make appointments.
- Index patients are invited into clinic to discuss results using the **Appendix 9.2 "Clinic invite letter to discuss gene testing results"**.
- Upon arrival in clinic patient is booked into clinic by reception and demographics are checked.
- FH nurse checks for previous bloods on the system, recording baseline and target levels.
- FH nurse greets patient and ascertains if patient understands reason for referral, explains reason for appointment.
- Genetic test report is explained and genetic mutation and implication discussed. Refer to BHF resource "**Life-with-familial-hypercholesterolaemia"** page 13 for guidance.
- Give the patient a copy of the genetic test report.
- Patient's cholesterol/lipid treatments discussed and noted.
- Educate about lifestyle, weight loss, activity, diet and smoking. Discuss areas for lifestyle improvements. Referral(s) made to clinic dietician, weight management and/ or smoking cessation as appropriate.
- Patient's pedigree is reviewed and cascade testing discussed with a view to identifying the 1st and 2nd degree relatives for cascade testing. Information from pedigree is used to identify relatives for cascade screening.
- FH nurse documents consent for cascade testing using the **Appendix 8.1 "Family form for cascade relative's contact details and cascade testing consent form"**. Patient's consent is obtained to store patient's details on PASS database, direct contact with relatives, if patient name can be used in direct contact letters, family tree to be shared with other family members.
- Indirect or direct contact method of contacting relatives for cascade testing is discussed.
- A combination of both direct and indirect contact method is used for the North, East and West Yorkshire and Humber (NEW Y&H) Familial Hypercholesterolaemia Identification and Cascade Testing Service with the index patients being given with the choice of their preferred method of contact. Refer to **"Indirect/Direct contact pathway"** for guidance.

- If patient prefers direct contact make a note of relatives details (names/addresses) on form. If the index prefers direct contact, it is recommended that the index patient needs to inform the relatives first and let them know that a member of the FH team will be contacting them and reason why.
- FH nurse to reconfirm with index patient two weeks after results appointment via telephone that initial contact has been made with relatives and the relative is happy to receive letters through the post.
- The FH nurse to post letters to relatives regarding cascade testing. Refer to **"Cascade Screening SOP"** for details.
- If the index prefers indirect contact, letters created on PASS are given to index case to pass onto relatives with a unique identifier code for the FH family. Refer to **Appendix 8.5 "Indirect contact letter to invite for cascade screening/segregation testing cover letter"** and **Appendix 8.6 "Indirect contact letter to invite for cascade screening/segregation testing reply form"**
- Clinic letter dictated using **Appendix 9.3** "**Positive genetics notification to GP, copied to Lipid Consultant with referral to lipid clinic for review (both index and cascade patients)"** and **Appendix 9.4 "Positive results letter for genetic test to patient".**
- Patient is referred to back to lipid clinic.
- Patient is discussed at regional MDT, treated to target lipid levels and then discharged back to primary care with clear management plan.
- If any identified first degree relatives are out of area or reside in an area where Familial Hypercholesterolaemia Identification and Cascade Testing Service has not been commissioned by their local CCG that have not signed up to the service please provide letter specifying reason as to why they cannot be offered service. Refer to Appendix **8.7 "First degree relative letter for cascades out of area /CCG's not commissioned cascade letter"**.
- FH nurse updates PASS system as per "**PASS SOP"**.

VUS genetic test reports

- Variants of Unknown Significance (VUS) need careful consideration for pathogenicity. All management plans discussed with clinical leads and GOSH labs prior to contacting patients to make appointments.
- Index patients are invited into clinic to discuss results using the **Appendix 9.2 "Clinic invite letter to discuss gene testing results"**. Upon arrival in clinic patient is booked into clinic by reception and demographics are checked.

- FH nurse checks for previous bloods on the system and documents them in the notes, recording baseline and target levels.
- FH nurse greets patient and ascertains if patient understands reason for referral, explains reason for appointment.
- Genetic test report is explained and genetic mutation and implication discussed. Refer to BHF resource "**Life-with-familial-hypercholesterolaemia"** page 13 for guidance.
- Give the patient a copy of the genetic test report.
- Patient's cholesterol/lipid treatments discussed and noted.
- Educate about lifestyle, weight loss, activity, diet and smoking. Discuss areas for lifestyle improvements. Referral(s) made to clinic dietician, weight management and/ or smoking cessation as appropriate.
- Advice cholesterol cascade in relatives or any other management plans as discussed with GOSH labs or lead clinician.
- Clinic letter dictated using the **Appendix 9.6 "Variant of Unknown significance letter to patient (index patient only) copied to Lipid Consultant and GP"**.
- Letter copied to patient notes, GP and Lipid/Cardiology Consultant.
- Patient is discussed at regional MDT, treated to target lipid levels and then discharged back to primary care with clear management plan.
- FH nurse updates PASS system as per "**PASS SOP"**.

Negative Mutation genetic test reports

- Negative mutation means clinical diagnosis of FH but no mutation identified.
- FH nurse posts the **Appendix 9.5 "Negative result letter for genetic test to patient (both index and cascade) copied to Lipid Consultant and GP"** and a copy of the genetic test report to the patient**.** Letter copied to patient notes, GP and Lipid/Cardiology Consultant.
- Patient is not seen in FH clinic for negative mutation reports but referred to back to lipid clinic.
- Patient is discussed at regional MDT, treated to target lipid levels and then discharged back to primary care with clear management plan.

Appendices:

1. **The modified Dutch Lipid Clinical Network scoring criteria for patients with a clinical diagnosis of FH**

Genotype scoring criteria for patients with a clinical diagnosis of FH Please note these criteria only apply for index cases, not family members of known genotype positive patients.		**Points (Please only circle a single highest score from each box)**
Family History	**1st/2nd degree relative:** · known with premature (<60yrs) CHD · known with premature (<45yrs) CHD · known with LDL-C > 4.9mmol/l (or total chol > 7.5mmol/l) · <18yrs with LDL-C > 4.0mmol/l (or total chol > 6.7mmol/l) ***Please specify relation to index case***	 1 2 1 2 ……
Physical Examination	·Tendon xanthomata (in patient **or 1st/2nd** degree relative) · Premature corneal arcus (no score for arcus senilis	6 4
Clinical History	· Patient with premature CHD (<45 yrs) · Patient with premature CHD (<50 yrs) · Patient with premature CHD (<60 yrs) · Patient with premature (<60yrs) strokes and/or peripheral vascular disease	4 3 2 1
Untreated or corrected LDL- Cholesterol Concentrations (mmol/l)	· LDL-C ≥ 8.5 · LDL-C 6.5 – 8.4 · LDL-C 5.0 – 6.4 · LDL-C 4.0 – 4.9 ***If untreated LDL- C values are unobtainable see attached sheet (Correction Factor Table) and calculate estimated value.***	
Fasting Triglycerides (mmol/l)	· Triglyceride 2.5 – 3.4 · Triglyceride 3.5 – 4.9 · Triglyceride ≥ 5.0 ***Please record in the narrative box any 2° causes that predispose to raised triglycerides, e.g. diabetes***	minus 2 minus 3 minus 4

Eligibility for FH genotyping is based on total points score

(Only one score from each box)

6 or above eligible for genotyping

5 or less usually not unless exceptional circumstances (if applicable, please state these in the clinical diagnosis and narrative box)

Forms which are unclear, incomplete or not eligible for genotyping will be returned to the requesting clinician and the sample stored for at least 6 months for possible future use.

2. LDL-C Correction Factor Table for patients on cholesterol lowering medication

If untreated LDL-C levels are unobtainable, then the following table can be used to estimate untreated values. To achieve this, multiply the treated LDL-C value by the appropriate correction factor.

Statin / dose (mg)	Correction Factor
Ezetimibe	
10 mg	1.2
Pravastatin	
10 mg	1.2
10 mg	1.3
10 mg	1.5
Pravastatin + Ezetimibe	
10 + 10	1.5
10 + 10	1.6
10 + 10	1.7
Simvastatin	
10	1.4
20	1.6
40	1.7
80	1.9
Simvastatin + Ezetemibe	
10 + 10	1.9
20 + 10	2.0
40 + 10	2.3
80 + 10	2.4
Atorvastatin	
10	1.6
20	1.8
40	2.0
80	2.2
Atorvastatin + Ezetemibe	
10 + 10	2.0
20 + 10	2.2
40 + 10	2.2
80 + 10	2.5
Rosuvastatin	
5	1.8
10	1.9
20	2.1
40	2.4
Rosuvastatin + Ezetimibe	
10 + 10	2.5
20 + 10	2.7
40 + 10	3.3

N.B. The above figures are calculated from a number of different research projects and clinical trials

3. **<u>Genetic Testing Consent Form for Familial Hypercholesteroalemia</u>**

For confirmation of diagnosis and cascade testing of family members

North, East and West Yorkshire & Humber (NEW Y&H) Familial Hypercholesterolaemia

Identification and Cascade Testing Service

Patient details

1. I consent for my blood sample to be analysed for genetic test for Familial Hypercholesterolaemia. I have had the opportunity to ask questions. I understand the implications of the test for me and the rest of the family.	**Yes/No**
2. I understand that if I choose not to have a genetic test for Familial Hypercholesterolaemia, my clinical care will not be affected.	**Yes/No**
3. I give consent to my GP and the specialist involved in the management of cholesterol to be informed of the results of my genetic tests.	**Yes/No**
4. I give consent for the specimen to be stored so that it can be retested for the same purpose should new tests or knowledge become available.	**Yes/No**
5. I consent to the results of my test(s) to be shared with other relatives and healthcare professionals providing testing for my relatives.	**Yes/No**

I have read and accept the above information.

Patient name Signature:

Date:

Consent obtained by Signature:

Date:

4. Joint genetic request form (GOSH)

North East Thames Regional Genetics Service Laboratory

Great Ormond Street Hospital for Children NHS

GENETIC TEST REQUEST FORM

SURNAME		FIRST NAME	
DATE OF BIRTH	GENETIC ID	NHS NUMBER	
SEX	ETHNIC ORIGIN	HOSPITAL NO	
PATIENT ADDRESS & POSTCODE			
GP NAME & ADDRESS		NHS / PRIVATE CCG CODE	
REFERRING CONSULTANT			
ADDRESS FOR REPORT		CONTACT NUMBER	

LAB REF:	
SAMPLE TYPE	URGENT / ROUTINE
DATE / TIME COLLECTED	DATE / TIME RECEIVED
SAMPLE TAKEN BY:	

REASON FOR REFERRAL
Please give clinical details

☐ **MOLECULAR GENETIC TEST (EDTA):**
Specify disease / gene test(s) and provide any relevant family history:

☐ DNA STORAGE *ONLY*
☐ DIAGNOSTIC TEST
☐ CARRIER TEST
☐ PREDICTIVE TEST
☐ NIPD

☐ **MICROARRAY (EDTA and LITHIUM HEPARIN):** Please confirm patient has one of the following:
☐ Developmental Delay ☐ Dysmorphism ☐ Multiple congenital abnormalities ☐ Epilepsy

Please provide full clinical details including family history above.

☐ **MICROARRAY FAMILY FOLLOW UP (EDTA AND LITHIUM HEPARIN)**
Please give name and laboratory number of index patient.

☐ **KARYOTYPING (LITHIUM HEPARIN)**

☐ Mosaicism suspected? please give details.

Rapid testing (LITHIUM HEPARIN (Infants under 3 months) for:
☐ Trisomy 21
☐ Trisomy 13 ☐ Trisomy 18
☐ Chromosomal sex
Please also select microarray or karyotype.

Consent is not required for DNA storage. It is the responsibility of the clinician to obtain consent before requesting a genetic test

5. Service document (GOSH)

North East Thames
Regional Genetics Service
Service Pack

Great Ormond Street Hospital for Children NHS
NHS Foundation Trust

Familial Hypercholesterolaemia

Contact details

Molecular Genetics Service
Level 6, Barclay House
37 Queen Square
London, WC1N 3BH
T +44 (0) 20 7762 6888
F +44 (0) 20 7813 8578

Samples required

- 5ml venous blood in plastic EDTA bottles (>1ml from neonates)
- A completed DNA request card should accompany all samples

Patient details

To facilitate accurate testing and reporting please provide patient demographic details (full name, date of birth, address and ethnic origin), details of any relevant family history and full contact details for the referring clinician

Introduction

Familial hypercholesterolaemia (FH) (MIM 143890) is a relatively frequent autosomal dominant condition, characterised clinically by elevations in low-density lipoprotein cholesterol (LDL-C), tendon xanthomata (TX) and premature coronary heart disease (CHD). Heterozygous FH has an incidence of around 1/500 individuals in the UK, and severe homozygous FH affects 1/1000 000 individuals. FH is genetically heterogeneous; however the primary genetic defect in FH is a mutation in the gene encoding the LDL-receptor (LDLR). LDLR has 18 exons and family specific mutations are found throughout the gene, although some recurrent mutations are reported. Large deletions or duplications encompassing one or more exons accounts for 5% of mutations in LDLR. A clinically indistinguishable disorder, familial defective apolipoprotein B100 (FDB), is due to a mutation in the gene encoding apolipoprotein B (APOB), which is one of the ligands of the LDL-receptor. The majority of FDB cases (2-5% of hypercholesterolaemic individuals) have a single mutation, p.Arg3527Gln. Mutations causing FH have also been identified in the PCSK9 and LDLRAP1 genes that account for a small proportion of cases.

Referrals

Referral criteria for testing are as determined by the Simon Broome Steering Committee:

a) Total cholesterol >7.5mmol/l or LDL-C >4.9mmol/l if >16yrs. If <16yrs total cholesterol >6.7mmol/l or LDL-C >4.0mmol/l

b) TX in patient or in first or second degree relative

c) Family history of myocardial infarction (MI) <60yrs in first degree relative or family history of MI <50yrs in second degree relative

d) Family history of total cholesterol >7.5mmol/l in first or second degree relative

Patients are separated into two groups, 'definite FH' and 'possible FH'. For a diagnosis of 'definite FH' both a) & b) must be present, but for 'possible' FH both a) & c) or a) & d) must be observed. Both groups are appropriate for genetic testing.

Mutation testing can be offered to the relatives of FH patients once a disease causing mutation has been identified.

Service offered

Analysis of of the LDLR, APOB, PCSK9 and LDLRAP1 genes by next generation sequencing (Agilent SureSelect and Illumina NextSeq). A minimum coverage of 30 reads is required to call a variant. In-house validation attributes a minimum sensitivity of 97.5% (with 95% confidence) for regions covered >30x. This assay is not currently validated to detect large deletions / duplications. LDLR gene dosage analysis is carried out using MLPA. All clinically relevant variants are confirmed by Sanger sequence analysis. Known benign polymorphisms and sequence variants which are unlikely to be pathogenic are not reported.

Mutation specific testing for previously identified mutations is available to other family members.

Target reporting time

8 weeks for a full mutation screen in an index case (next generation sequencing and MLPA). 2 weeks for familial mutation testing.

Version 8

6. **FAMILIAL HYPERCHOLESTEROLAEMIA APPOINTMENT WHAT TO EXPECT**

North, East and West Yorkshire & Humber (NEW Y&H)

Familial Hypercholesterolaemia Identification and Cascade Testing Service

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- Consultations will normally last between 45-60 minutes.

- The Familial Hypercholesterolaemia (FH) nurse will explain the condition in detail but feel free to bring any questions or concerns.

- **Family tree** – we will spend some time drawing a family tree, which can give us valuable information. It may be helpful for us to have medical details of your immediate family. Including names, dates of birth, contact details (address), and any cardiac/cholesterol related history.

- **Blood sample** – please note that we may need to take a blood sample but you are not required to fast.

- For information on Familial Hypercholesterolaemia (FH) prior to appointment please visit www.bhf.org.uk or www.heartuk.org.uk.

7. Index patient clinic letters (via PASS template)

7.1 Index patient clinic invite letter template

North, East and West Yorkshire & Humber (NEW Y&H)

Familial Hypercholesterolaemia Identification and Cascade Testing Service

Consultant **NHS no:**

Contact details

Familial Hypercholesterolaemia Nurse Specialist

Contact details

Local Trust details

Date: dd/mm/yyyy

Dear XXXX,

I am writing to you because you have been referred to the North, East and West Yorkshire & Humber (NEW Y&H) Familial Hypercholesterolaemia Identification and Cascade Testing Service, regarding your cholesterol levels and family history of heart disease. You were referred to our service by Dr XXXXXXXX, who is seeing you due to your raised cholesterol levels.

It is possible you may have an inherited condition called Familial Hypercholesterolaemia (FH) which causes high levels of cholesterol in your blood. It can increase your risk of developing heart disease at an early age and a service has now commenced to assess and support individual/families with this condition.

If this is something you would be interested in discussing further, please call us on **(Telephone)** to arrange an appointment. If there is no one in the office you can leave a message on the answer phone. Please give your name and contact telephone number and we will call you back as soon as possible.

We ask that you call us within **two weeks** of receipt of this letter. Please note if we have not heard from you within **four weeks** we will send you a reminder.

Yours sincerely,

Familial Hypercholesterolaemia Nurse Specialist

Telephone:

Encl:

FH appointment what to expect doc

CC. Dr (Lipid Consultant)

7.2 Index first reminder letter template

North, East and West Yorkshire & Humber (NEW Y&H)
Familial Hypercholesterolaemia Identification and Cascade Testing Service

Consultant **NHS no:**

Contact details

Familial Hypercholesterolaemia Nurse Specialist

Contact details

Local Trust details

Date: dd/mm/yyyy

Dear XXXX,

We have recently written to you asking you to call us to arrange an appointment with the North, East and West Yorkshire & Humber (NEW Y&H) Familial Hypercholesterolaemia Identification and Cascade Testing Service, regarding your cholesterol levels and family history of heart disease. We are recontacting you as we have not heard from you.

It is possible you may have an inherited condition called Familial Hypercholesterolaemia (FH) which causes high levels of cholesterol in your blood. It can increase your risk of developing heart disease at an early age and a service has now commenced to assess and support individual/families with this condition.

If this is something you would be interested in discussing further, please call us on **(Telephone)** to arrange an appointment. If there is no one in the office you can leave a message on the answer phone. Please give your name and contact telephone number and we will call you back as soon as possible.

We ask that you call us within **two weeks** of receipt of this letter. Please note that if we do not hear anything from you further we will presume you are not interested in discussing this and will be discharged from the waiting list. You will however receive a final letter reconfirming this.

Yours sincerely,

Familial Hypercholesterolaemia Nurse Specialist

Telephone:

CC. Dr (Lipid Consultant)

7.3 Index final reminder letter template

North, East and West Yorkshire & Humber (NEW Y&H)
Familial Hypercholesterolaemia Identification and Cascade Testing Service

Consultant **NHS no:**

Contact details

Familial Hypercholesterolaemia Nurse Specialist

Contact details

Local Trust details

Date: dd/mm/yyyy

Dear XXXX,

We have recently written to you asking you to call us to arrange an appointment with the North, East and West Yorkshire & Humber (NEW Y&H) Familial Hypercholesterolaemia Identification and Cascade Testing Service, regarding your cholesterol levels and family history of heart disease. You were referred to our service by Dr XXXXXXXX, who is seeing you due to your raised cholesterol levels.

We have sent you previous reminder. As you have not contacted us we assume that you no longer require the appointment, and you have been discharged from our waiting list. If you have contacted us in the last few days and arranged an appointment please disregard this letter.

This does not affect your Lipid clinic appointments.

If you still require an appointment, or anytime in the future, please contact us on **(Telephone)** to arrange an appointment.

Yours sincerely,

Familial Hypercholesterolaemia Nurse Specialist

Telephone:

8. Cascade patient clinic letters (via PASS template)

8.1 Family form for cascade relative's contact details and cascade testing consent form

North, East and West Yorkshire & Humber (NEW Y&H)

Familial Hypercholesterolaemia Identification and Cascade Testing Service

Name: …… Date of birth: ……

FH Nurse: ……..

Patient details: ……..

Today's date: ……

Telephone/Day: …… Evening: ……

Section 1: There are two methods of carrying out family testing

Direct Contact: The FH service will attempt to contact your relatives with the information that you provide to find out whether or not they wish to be tested. This is done by sending them letters through the post. We recommend that you speak to your relatives and let them know that a member of the FH team will be contacting them and why. If you don't want your relatives to know that you have FH, we can withhold your name.

Indirect Contact: You take responsibility for contacting your relatives. We can help you by providing you with letters/information to give to them. If we don't hear from them, we may ask you to check whether or not they would like to be tested.

A combination of both methods can be used.

Section 2: Contacting relatives

Please provide details for all of your blood relatives, and select how you would like them to be contacted: We can provide an indirect letter for you to pass to them, or we can contact them directly if you provide their full address. Contact may not be possible/appropriate following assessment by the FH Team.

Full name	Date of Birth	Relationship to you	Type of contact: please select one for each relative				
			INDIRECT CONTACT			DIRECT CONTACT	No contact
			Indirect contact	If so, letter taken?	Lives in Yorkshire? Y/N	Please give full address	

Full name	Date of Birth	Relationship to you	Type of contact: please select one for each relative			
			INDIRECT CONTACT		DIRECT CONTACT	No contact
			Indirect contact	If so, letter taken?	Please give full address	

Section 4: Consent for family testing

Please tick the relevant boxes and sign below

1) I consent for the information on this form to be placed on a secure NHS database YES ☐ NO ☐

2) I consent to direct contact YES ☐ NO ☐

3) If direct contact has been chosen: I am happy for my name to be used in the direct contact letters YES ☐ NO ☐

4) I consent for my family tree to be shared with other family members who seek FH testing YES ☐ NO ☐

Please print your name and sign below:

_____ _____ _____

Full Name (please print) **Date** **Signature**

Please return in the SAE

(**FH nurse address**)

8.2 Direct contact letter to invite for cascade screening/segregation testing appointment

North, East and West Yorkshire & Humber (NEW Y&H)

Familial Hypercholesterolaemia Identification and Cascade Testing Service

Consultant **NHS no:**

Contact details

Familial Hypercholesterolaemia Nurse Specialist

Contact details

Local Trust details

Date: dd/mm/yyyy

Dear XXXX,

I am writing to you on behalf of the North, East and West Yorkshire & Humber (NEW Y&H) Familial Hypercholesterolaemia Identification and Cascade Testing Service.

I am writing to you because a member of your family has been found to have a genetic condition called Familial Hypercholesterolaemia (FH). This is an inherited condition caused by a gene alteration that results in high cholesterol from birth and can be passed down through families. High cholesterol leads to a greater risk of premature heart disease if left untreated but this extra risk can be almost eliminated with early identification and simple treatment. We are offering family testing to all blood relatives of patients with FH to find out which other members of the family also have the same gene alteration causing high cholesterol. You will be asked to have blood tests to see if you have the special form of high cholesterol that your relative has.

To arrange an appointment you can either see your GP who can refer into the service. **Edit text for direct access.**

Please phone us if you have any questions at all or would like to discuss this further. If you live outside North, East and West Yorkshire & Humber area please take this letter to your GP and ask them to refer you to your local lipid clinic. We hope that you will take part in the testing of family members but if you decide not to you should ask your GP to arrange a cholesterol test. To do this, please take this letter to your GP.

We ask that you call us within **two weeks** of receipt of this letter. Please note if we have not heard from you within **four weeks** we will send you a reminder.

Yours sincerely,

Familial Hypercholesterolaemia Nurse Specialist

Telephone:

Encl:

FH appointment what to expect doc

8.3 Direct contact letter to invite for cascade screening/segregation testing appointment first reminder

North, East and West Yorkshire & Humber (NEW Y&H)

Familial Hypercholesterolaemia Identification and Cascade Testing Service

Consultant **NHS no:**

Contact details

Familial Hypercholesterolaemia Nurse Specialist

Contact details

Local Trust details

Date: dd/mm/yyyy

Dear XXXX,

We have recently written to you asking you to call us to arrange an appointment with the North, East and West Yorkshire & Humber (NEW Y&H) Familial Hypercholesterolaemia Identification and Cascade Testing Service, as your relative has been found to have a genetic condition called Familial Hypercholesterolaemia (FH). We are recontacting you as we have not heard from you.

It is possible you may have an inherited condition called Familial Hypercholesterolaemia (FH) which causes high levels of cholesterol in your blood. It can increase your risk of developing heart disease at an early age and a service has now commenced to assess and support individual/families with this condition.

If this is something you would be interested in discussing further, please call us on **(Telephone)** to arrange an appointment. If there is no one in the office you can leave a message on the answer phone. Please give your name, contact telephone number and the reference number from the top of this letter and we will call you back as soon as possible.

D Narayanan March 2017

We ask that you call us within **two weeks** of receipt of this letter. Please note that if we do not hear anything from you further we will presume you are not interested in discussing this and will be discharged from the waiting list. You will however receive a final letter reconfirming this.

Yours sincerely,

Familial Hypercholesterolaemia Nurse Specialist

Telephone:

8.4 Direct contact letter to invite for cascade screening/segregation testing appointment final reminder

North, East and West Yorkshire & Humber (NEW Y&H)

Familial Hypercholesterolaemia Identification and Cascade Testing Service

Consultant **NHS no:**

Contact details

Familial Hypercholesterolaemia Nurse Specialist

Contact details

Local Trust details

Date: dd/mm/yyyy

Dear XXXX,

We have recently written to you asking you to call us to arrange an appointment with the North, East and West Yorkshire & Humber (NEW Y&H) Familial Hypercholesterolaemia Identification and Cascade Testing Service, as your relative has been found to have a genetic condition called Familial Hypercholesterolaemia (FH).

We have sent you previous reminder. As you have not contacted us we assume that you no longer require the appointment, and you have been discharged from our waiting list. If you have contacted us in the last few days and arranged an appointment please disregard this letter.

If you still require an appointment, or anytime in the future, please contact us on (**(Telephone)** to arrange an appointment.

Yours sincerely,

Familial Hypercholesterolaemia Nurse Specialist

Telephone:

8.5 Indirect contact letter to invite for cascade screening/segregation testing cover letter

North, East and West Yorkshire & Humber (NEW Y&H)

Familial Hypercholesterolaemia Identification and Cascade Testing Service

Consultant

Contact details

Familial Hypercholesterolaemia Nurse Specialist

Contact details

Local Trust details

Date: dd/mm/yyyy

Reference number:

Please quote this number when contacting us: FH Family

Dear ……

We are the Familial Hypercholesterolaemia (FH) Nurse Specialists working across North, East and West Yorkshire and Humber region. We have asked your relative to pass this letter on to you.

Your relative has been found to have a genetic condition called Familial Hypercholesterolaemia (FH). This is an inherited condition caused by a gene alteration that results in high cholesterol from birth and can be passed down through families. High cholesterol leads to a greater risk of premature heart disease if left untreated but this extra risk can be almost eliminated with early identification and simple treatment.

We are offering family testing to all blood relatives of patients with FH to find out which other members of the family also have the same gene alteration causing high cholesterol. You will be

asked to have blood tests to see if you have the special form of high cholesterol that your relative has.

To arrange an appointment you can either see your GP who can refer into the service or contact us on **xxxx xxxxxx** directly.

Please phone us if you have any questions at all or would like to discuss this further. If you live outside the North, East and West Yorkshire and Humber region please take this letter to your GP and ask them to refer you to your local lipid clinic. Most genetics centres are able to provide testing once a gene alteration has been identified in the family. We hope that you will take part in the testing of family members but if you decide not to you should ask your GP to arrange a cholesterol test. To do this, please take this letter to your GP.

Yours sincerely

FH Nurse Specialists.

8.6 Indirect contact letter to invite for cascade screening/segregation testing reply form

Familial Hypercholesterolaemia (FH) Cascade Testing - Reply Form

Reference number:

Name:

DOB……

Address:……

Postcode:……Telephone Number:.....

GP Name:…….

GP Address:…….

For the purposes of generating this reply form we have added your name and date of birth to a secure NHS database. In line with data protection policy your details will be removed if you do not respond within two year. If you would like your details to be removed immediately, please ring 0191 5410181.

Please initial if you give consent for your information to be held on a secure FH National

Database ☐

I understand that someone in my family has high cholesterol and you would like to talk to me about having a genetic test to see if I have inherited the gene alteration identified in my relative.

I **would/would not** (delete as appropriate) like to know more about this

(Please tick one box)

☐ I would like to receive an appointment in the post.

☐ I would like to be telephoned to arrange a convenient appointment on

Home phone number……..

Work phone number……..

Mobile phone number……..

☐ I do not want to be contacted at this time. I would like to be contacted in ….. months.

☐ I do not want to be contacted now or in the future.

Signature **Date**

Please return to: **FH nurses, North, East and West Yorkshire & Humber (NEW Y&H) Familial Hypercholesterolaemia Identification and Cascade Testing Service, xxxxxxx**

8.7 First degree relative letter for cascades out of area /CCG's not commissioned cascade letter

North, East and West Yorkshire & Humber (NEW Y&H)

Familial Hypercholesterolaemia Identification and Cascade Testing Service

York Teaching Hospital Foundation Trust,

Wigginton Road, York, YO31 8HE

Tel:

Fax:

Ref:

Dear Mr/Mrs

This is a letter for you to hand to your GP if you wish to be referred to your local Familial Hypercholesterolaemia (FH) or genetics service, for genetic testing of FH. Please complete your details below prior to handing this letter to your GP.

For the purpose of generating this letter your name and date of birth have been added to a secure NHS database. If you would like your details to be removed immediately, please ring xxxxxxxxxxx

To whom it may concern

Name……:

Date of birth:…….

Address:……

Postcode:…… Telephone number:……..

GP Name:……..

The Familial Hypercholesterolaemia (FH) service in the North East has identified your patient as a first degree relative of someone with FH. This means they have a 50% probability of also being diagnosed with FH.
As your patient lives outside of North, East and West Yorkshire and Humber region, we recommend that they are referred to their local FH or genetic service to be offered testing for FH.
If genetic testing is not available at your local FH or genetic service we recommend they have a fasting lipid profile measured. If they have raised LDL levels they should be referred to their local lipid clinic to ensure appropriate treatment and management. This should include cascade testing of family members. If you have any queries, please contact The FH service on the above number.

Yours sincerely
FH Nurse Specialist
D Narayanan March 2017
53

9. Clinic letters and results of genetic testing and cascade screening (via PASS template)

9.1 Clinic letter to Patient (both Index and cascade) copied to Lipid Consultant via PASS Template

North, East and West Yorkshire & Humber (NEW Y&H)

Familial Hypercholesterolaemia Identification and Cascade Testing Service

Consultant **NHS no:**

Contact details

Familial Hypercholesterolaemia Nurse Specialist

Contact details

Local Trust details

Date: dd/mm/yyyy

Dear XXXX,

It was lovely to meet you when you came to the North, East and West Yorkshire & Humber (NEW Y&H) Familial Hypercholesterolaemia Identification and Cascade Testing Service clinic. The referral for the clinic appointment was to discuss the diagnosis of Familial Hypercholesterolaemia (FH), the implications of this, including possible genetic testing. This letter is to summarise the main points that we discussed.

Familial Hypercholesterolaemia

I started our appointment explaining what FH is, using the "**BHF booklet"** which I gave to you. As you remember, I explained that if FH is appropriately treated with cholesterol lowering medication and a healthy lifestyle, the excess LDL (bad) cholesterol and the extra risk of developing heart disease associated with FH can be virtually eliminated, so it is important to be diagnosed and treated. Therefore informing other family members of their risk is also important.

Family History

FH is a common genetic condition affecting at least 1 in 500 people. When I illustrated your family history in a diagram, we identified and discussed the family members in your family that need to be tested for FH as well.

FH Genes and their Inheritance

We talked about the possible genes that are affected by FH and how these are inherited. If there is an altered FH gene in the family, we would assume that the people who have been affected with high cholesterol are likely to carry one normal copy of the gene and one altered copy.

Genetic Testing (testing for this gene alteration)

We discussed the possibility of testing for this gene alteration, and its implications for yourself and your family. You filled in the **"Genetic test consent form**" and I obtained a blood sample to be sent off for testing. As you remember the results can take in the region of 2 months and I will contact you once we have received these results.

Lifestyle Education and Plan

We discussed diet and lifestyle.

If you have any questions at all please do not hesitate to contact me **(Telephone).**

Yours sincerely,

Familial Hypercholesterolaemia Nurse Specialist

Telephone:

CC. Dr (Lipid Consultant)

9.2 Clinic invite letter to discuss gene testing results (both index and cascade patients)

North, East and West Yorkshire & Humber (NEW Y&H)

Familial Hypercholesterolaemia Identification and Cascade Testing Service

Consultant **NHS no:**

Contact details

Familial Hypercholesterolaemia Nurse Specialist

Contact details

Local Trust details

Date: dd/mm/yyyy

Dear XXXX,

This letter is to follow up from your visit to the North, East and West Yorkshire & Humber (NEW Y&H) Familial Hypercholesterolaemia Identification and Cascade Testing Service clinic in which you had a blood sample taken to look for the gene change that causes your high cholesterol.

Your results are now available. Please could you call us on **(Telephone)** to arrange a mutually convenient appointment time to discuss these results. We ask you to call us within **two weeks** of receipt of this letter.

Due to the complexity of the results it is not always possible to discuss these results over the phone or via a letter.

Yours sincerely,

Familial Hypercholesterolaemia Nurse Specialist

Telephone:

9.3 Positive genetics notification to GP, copied to Lipid Consultant with referral to lipid clinic for review (both index and cascade patients)

Dear Dr

Re: Patient details

The above named patient recently attended our genetic screening clinic for Familial Hypercholesterolaemia (FH). The results have now been received and subsequently confirm that a genetic mutation known to cause FH has been found. A copy of the results is attached for your records.

Having been diagnosed with FH it is very likely that your patient has a number of relatives who may be affected by FH. FH has an autosomal dominant pattern of inheritance meaning that each child of a parent with FH has a 50% chance of inheriting the mutation. As part of our cascade screening protocol, in the first instance, we will now invite any first degree relatives for genetic screening. We would also advise that any second and third degree relatives initially have their lipid profile checked at their GP surgery.

In line with NICE guidance for the management of FH patients, we would recommend that all patients with a confirmed genetic diagnosis of FH receive an in depth annual review with a specialist in FH.

The patient will be referred to the lipidologist Dr.xxxxx for further management.

http://publications.nice.org.uk/identification-and-management-of-familial-hypercholesterolaemia-cg71

Yours Sincerely,

Cc Lipid consultant

Cc GP

9.4 Positive results letter for genetic test to patient

North, East and West Yorkshire & Humber (NEW Y&H)

Familial Hypercholesterolaemia Identification and Cascade Testing Service

Consultant **NHS no:**

Contact details

Familial Hypercholesterolaemia Nurse Specialist

Contact details

Local Trust details

Date: dd/mm/yyyy

Dear XXXX,

As discussed at the North, East and West Yorkshire & Humber (NEW Y&H) Familial Hypercholesterolaemia Identification and Cascade Testing Service clinic today you have been identified as having a mutation (gene alteration) in the gene for Familial Hypercholesterolaemia (FH).

This is helpful because it confirms the clinical diagnosis of FH and reinforces the need for you to maintain a healthy lifestyle and to continue with your lipid lowering treatment. There is strong evidence to support the effectiveness of these treatments in reducing the risk of heart and vascular disease.

Any medical treatment you are receiving will remain unchanged and we advise that you continue taking any medication prescribed to you. A copy of the results has been forwarded to your GP and we will arrange for review in specialist lipid clinic for on-going management and follow up.

This result also means that this testing can be offered to other members of your family who may be at risk of having FH. The **"Cascade testing consent form"** that you completed will assist with family cascade screening process.

I explained the process and approximate timeframes of family cascade screening and you kindly agreed to give the provided cascade screening packs to your relatives and pre-alert them that we may be in touch **(amend if direct contact).**

If you have any further questions following our discussion please do not hesitate to contact me **(Telephone).**We will see you for review in the lipid clinic in due course.

Yours sincerely,

Familial Hypercholesterolaemia Nurse Specialist

Telephone:

9.5 Negative result letter for genetic test to patient (both index and cascade) copied to Lipid Consultant and GP

North, East and West Yorkshire & Humber (NEW Y&H)

Familial Hypercholesterolaemia Identification and Cascade Testing Service

Consultant

Contact details

Familial Hypercholesterolaemia Nurse Specialist

Contact details

Local Trust details **NHS no:**

Date: dd/mm/yyyy

Dear XXXX,

I am writing to you following your visit to the North, East and West Yorkshire & Humber (NEW Y&H) Familial Hypercholesterolaemia Identification and Cascade Testing Service clinic in which you gave a blood sample for DNA testing. Your results have come back and there has been no identified, specific genetic alteration (also called mutation) to explain the cause of your high cholesterol.

Any medical treatment you are receiving will remain unchanged and we advise that you continue taking any medication prescribed to you. A copy of the results has been forwarded to your GP and we will arrange for review in specialist lipid clinic for on-going management and follow up.

It also means that we will not be able to use a genetic blood test for other members of your family. If there is high cholesterol inherited in the family, we would advise that other family members should be assessed using cholesterol blood tests. They should contact their own GP for this.

Please do not hesitate to contact me if you or your family have any further queries.

Yours Sincerely,

Familial Hypercholesterolaemia Nurse Specialist

Telephone:

CC. GP

CC. Dr (Lipid Consultant)

9.6 Variant of Unknown significance letter to patient (index patient only) copied to Lipid Consultant and GP

North, East and West Yorkshire & Humber (NEW Y&H)

Familial Hypercholesterolaemia Identification and Cascade Testing Service

Consultant **NHS no:**

Contact details

Familial Hypercholesterolaemia Nurse Specialist

Contact details

Local Trust details

Date: dd/mm/yyyy

Dear XXXX,

As discussed at the North, East and West Yorkshire & Humber (NEW Y&H) Familial Hypercholesterolaemia Identification and Cascade Testing Service clinic today we identified a change in the DNA sequence for the Low Density Lipoprotein (LDL) Cholesterol receptor but the clinical significance of this is as yet unclear.

In some people the laboratory can detect a change in the DNA sequence, which has not been described before and therefore we cannot be sure whether or not this is causing Familial Hypercholesterolaemia (FH) in your case.

At present, we are unable to offer any further genetic testing for yourself or your family to clarify the result. However, as discussed, I will be contacting family members to identify whether they have raised cholesterol and advise them accordingly.

Any medical treatment you are receiving will remain unchanged and we advise that you continue taking any medication prescribed to you. A copy of the results has been forwarded to your GP and we will arrange for review in specialist lipid clinic for on-going management and follow up.

If you have any further questions following our discussion please do not hesitate to contact me **(Telephone).** We will see you for review in the lipid clinic in due course.

Yours sincerely,

Familial Hypercholesterolaemia Nurse Specialist

Telephone:

CC. Dr (Lipid Consultant)

CC. GP

10. FH Genetic testing invoicing letter

North, East and West Yorkshire & Humber (NEW Y&H) Familial Hypercholesterolaemia

Identification and Cascade Testing Service

Date:

Specimen Reception

Level 5, Barclay House, Great Ormond Street Hospital

37 Queen Square, London

WC1N 3BH

To whom it may concern,

Patient initials _____ PASS database no: _____

Please note the invoicing address details for the attached North, East and West Yorkshire & Humber (NEW Y&H) Familial Hypercholesterolaemia Identification and Cascade Testing Service sample as below:

Amanda Mullin

Deputy Directorate Manager – cardiology

Ward 37

York Teaching Hospital Foundation Trust, Wigginton Road, York

YO31 8HE

Reference PO: 4111130241

Please cost and invoice accordingly.

Thanks,

PLEASE SEND A COPY OF COMPLETED LETTER WITH EACH SAMPLE

11. SOP Training Log

	Name of Staff	Job Title & Department	Training date	I confirm that I understand & agree to work to this SOP (signed)
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				

11				
12				
13				
14				
15				

References:

1. Nordestgaard et al. Familial Hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease. Consensus Statement of the European Atherosclerosis Society. European Heart Journal (2013); 34, 3478-3490.

2. Dorsch et al. Familial Hypercholesterolaemia is underdiagnosed after AMI. British Medical Journal. 2001; 322: 111.

3. Khera et al. Diagnostic Yield and Clinical Utility of Sequencing Familial Hypercholesterolaemia Genes in Patients with Severe Hypercholesterolaemia. JACC. 2016; 67: 2578-2589.

4. Brice P et al. Familial Hypercholesterolaemia: A pressing issue for European health care. Atherosclerosis. 231 (2013) 233-226.

5. National Institute for Health and Clinical Excellence (NICE). Familial Hypercholesterolaemia. Quality Standard 41. London: NICE; 2013.

6. National Institute for Health and Clinical Excellence (NICE). Familial Hypercholesterolaemia. Clinical Guidelines 71. London: NICE; 2008.

7. Neely RDG. The importance of early diagnosis: how to identify patients with FH for diagnosis and referral. Prim Care Cardiovasc Journal 2014; 7:31-35.

8. Minhas R et al. Controversies in familial hypercholesterolaemia: recommendations of the NICE guideline development group for the identification and management of familial hypercholesterolaemia. Heart 2009; 95: 584-587.

9. National Institute for Health and Clinical Excellence (NICE). Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. Clinical Guideline 181. London: NICE; 2014.

10. Newson AJ & Humphries SE. Cascade testing in familial hypercholesterolaemia: how should family members be contacted? European Journal of Human Genetics 2005; 13: 401-408.

Acknowledgements

- NHS Wales Familial hypercholesterolaemia and family cascade testing. Map of Medicine > Cardiology > Familial hypercholesterolaemia 2010.
- Guidelines for the Bristol and Bath Familial Hypercholesterolaemia (FH) Cascade Screening Service.
- South Yorkshire and North Derbyshire Familial Hypercholesterolaemia (FH) Cascade Screening Service Standard Operating Procedures.
- NHS Highland cascade screening service Standard Operating Procedures.