Lowering Cholesterol.

Saving Lives.

Tackling Cholesterol Together

Health Innovation East

Part of the Health Innovation Network

ACCELERATED ACCESS COLLABORATIVE

HEART UK THE CHOLESTEROL CHARITY

NHS

NHS East Genomic Laboratory Hub

NHS Cambridge University Hospitals NHS Foundation Trust

NHS Norfolk and Norwich University Hospitals NHS Foundation Trust

Familial Hypercholesterolaemia (FH): Identification - where to begin and whom to test

Paul Flynn
Consultant in Metabolic Medicine Cambridge University Hospitals NHS FT

Javier Gomez
Consultant Chemical Pathologist / Service Lead Clinical Biochemistry and Immunology EPA Norfolk and Norwich University Hospital

Kate Downes
Clinical Scientist / Lead Scientist for Rare and Inherited Disease East Genomic Laboratory Hub

In a recent Lipid Clinic….

45 year old male
Had presented aged 41 with angina during an ultramarathon
Paternal grandfather had an MI (?age)
Father has been on statins since his 40s
Total Cholesterol was 8.0 mmol/L (estimated LDL-C 6.0)
Stopped smoking in 2007

Went on to have a PCI to his left main stem

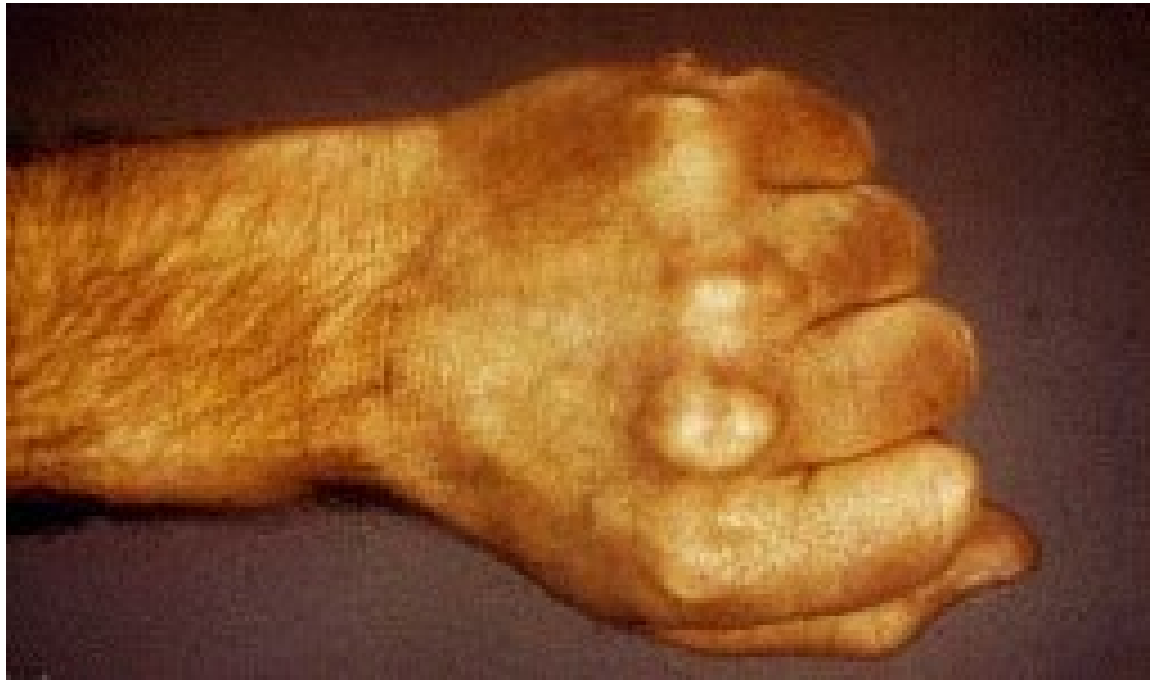
Diagnosis: likely monogenic Familial Hypercholesterolaemia (FH)

Could this have been prevented/delayed?

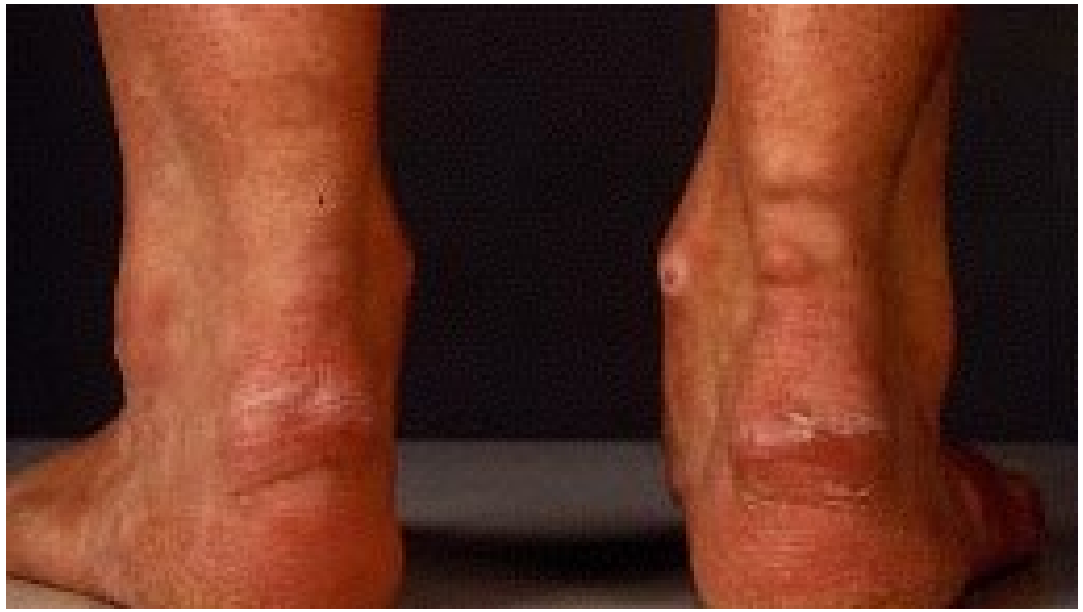
Clinical Features of Familial Hypercholesterolaemia

- Xanthomatosis
- Hypercholesterolaemia
- Premature cardiovascular disease
- Autosomal co-dominant inheritance

Extensor Tendon Xanthomas



Achilles Tendon Xanthomas



Hypercholesterolaemia

Genotype	Age	TC	LDL-C	HDL-C	Tgs
Normal	< 20	4.52 ± 0.72	2.84 ± 0.64	1.37 ± 0.33	0.68 ± 0.28
Heterozygous	< 20	7.73 ± 1.63	6.23 ± 1.55	1.11 ± 0.31	0.93 ± 0.58
Homozygous	< 20	17.5 ± 4.39	16.1 ± 4.13	0.88 ± 0.26	1.14 ± 0.58

From Kwiterovich et al. J Clin Invest 1974;53:1237

Premature Ischaemic Heart Disease in Heterozygous FH

	Incidence of IHD (%)		Mortality from IHD (%)	
Age (yr)	Men	Women	Men	Women
<30	5	0	0	0
30-39	24	0	7	0
40-49	51	12	24	0
50-59	85	58	54	15
60-69	100	74	78	15

Slack J Lancet; 1969ii:1380-2

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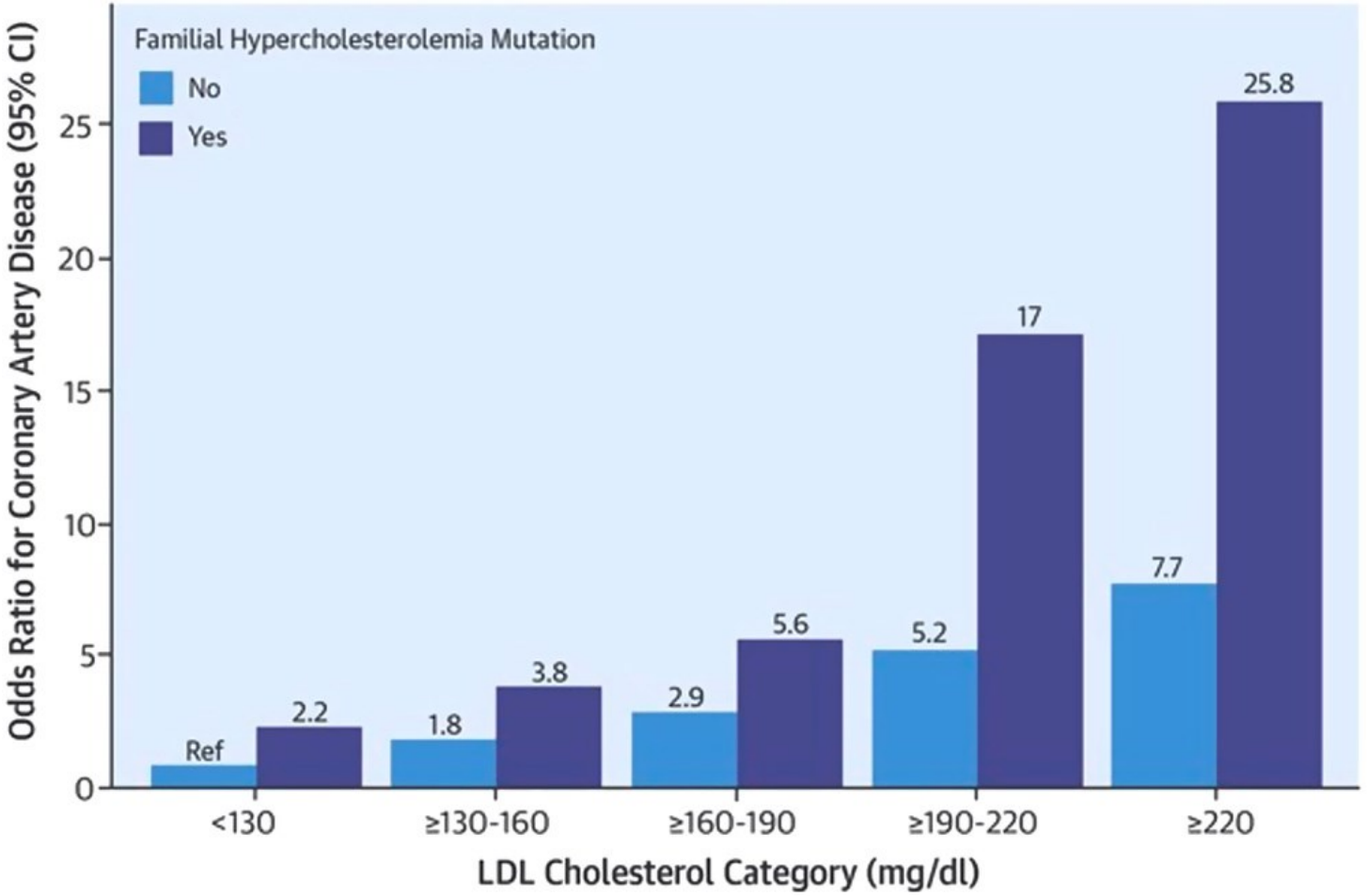
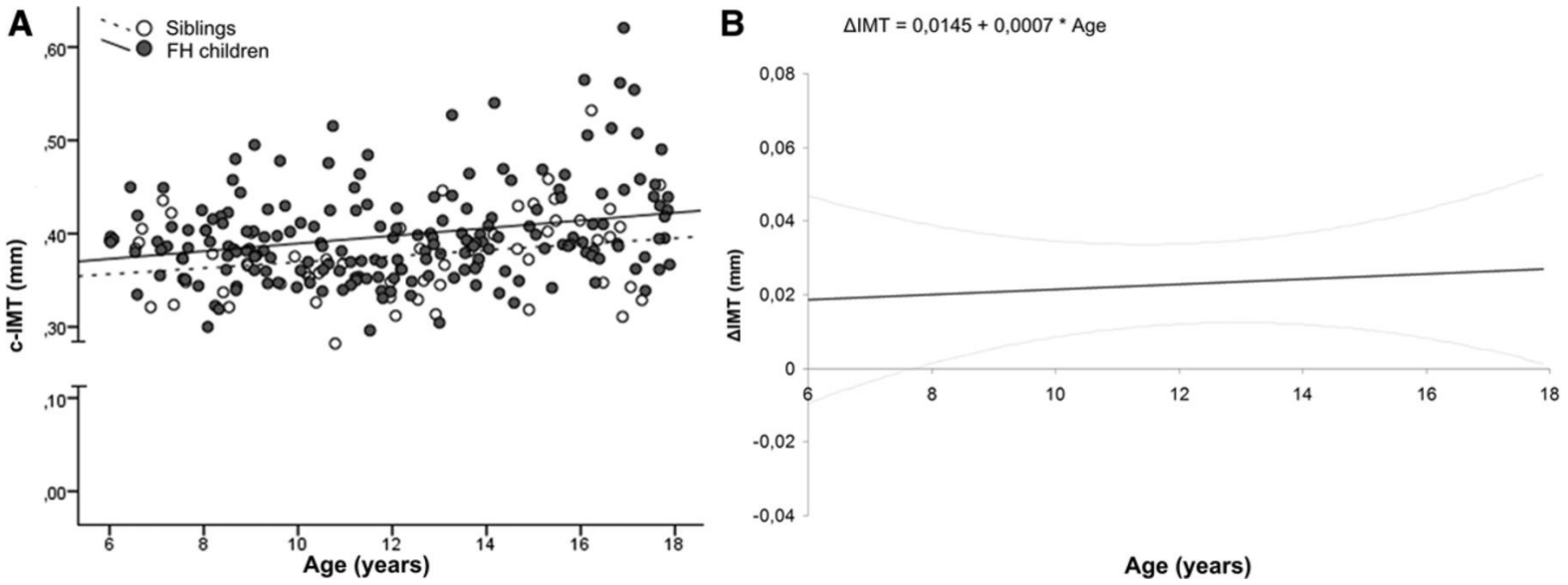
FH versus Hypercholesterolaemia



. Lan, S.R. Recent advances in the management and implementation of care for familial hypercholesterolaemia. Pharm Research; 2023

Premature Atherosclerosis in HeFH



Kusters DM, Wiegman A, Kastelein JJP & Hutten BA. Circ Res 2014;114:307-310

FH: Prevalence

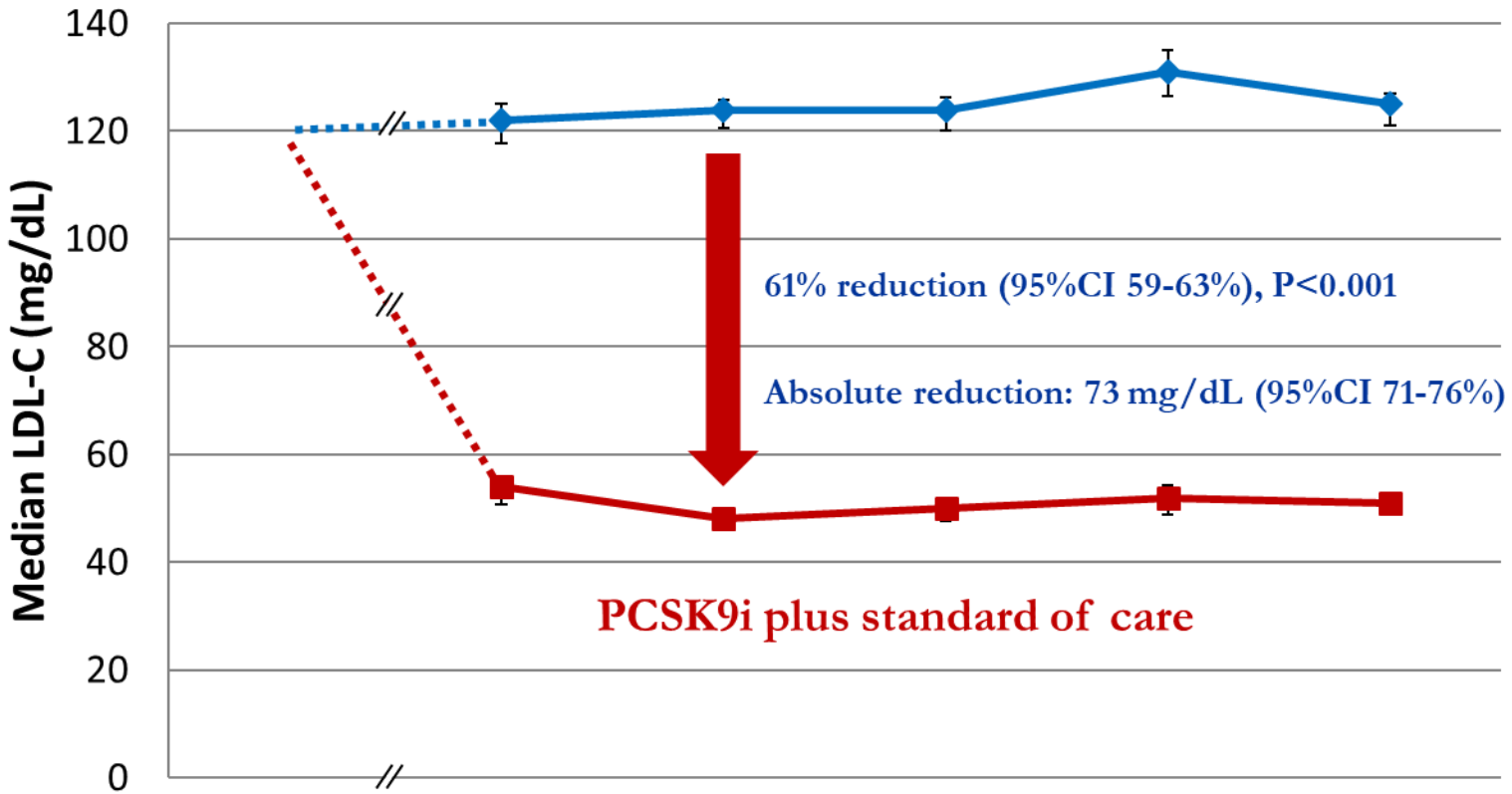
- Heterozygous
  - Europe, USA and Japan 1 in 250
  - Lebanon, South Africa, French speaking Canada and Lithuanian Jews
    Founder gene effect

- Homozygous
  - Europe, USA and Japan 1 in $1x10^6$ and the majority of these are compound heterozygotes

FH: Treatment

- Dietary fat restriction, bile acid sequestrants
- Statins
- Ezetimibe
- Alirocumab/Evolocumab
- Inclisiran
- Bempedoic Acid

PSCK9 inhibitors

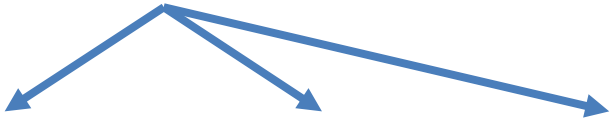


	Baseline (Parent study)	4 weeks (OSLER)	12 weeks	24 weeks	36 weeks	48 weeks
	N=4465	N=1258	N=4259	N=4204	N=1243	N=3727
Abs. reduction (mg/dL)		60.4	73.4	70.4	72.7	70.5
Abs. reduction (mmol/L)		1.56	1.90	1.82	1.88	1.82

Sabatine et al. N Engl J Med. 2015 Apr 16;372(16):1500-9 (Suppl.):1-21

Cholesterol lowering drugs in 2024

First optimise lifestyle/Statin/Ezetimibe & fully treat 2° causes, then:



	Alirocumab/ Evolocumab	Inclisiran	Bempedoic Acid
Mode of action	PCSK9i mAb	PCSK9 mRNAi	ATP citrate lyase inhibitor, prodrug
Administration	2/52 sc injection (by patient)	6/12 sc injection (by HCP)	Daily tablet (by patient)
LDL-C reduction	~ 60%	~ 50%	~ 25%
Clinical outcome	Reduces CV risk	Awaited	Reduces CV risk
Primary prevention	Only if HeFH & LDL-C > 5.0	Not licensed	If felt will help, and no statin
Secondary prevention	LDL-C > 4.0, or 3.5 if very high risk	LDL-C > 2.6	If felt will help, and no statin
Setting	Secondary care only	Primary and Secondary care	Secondary and Primary care

In a recent Lipid Clinic....

74 year old male
Had participated in the 100,000 genomes project
Had been found to have an FH causing genetic variant

No history of any atherosclerotic cardiovascular disease

Premature Ischaemic Heart Disease in Heterozygous FH

	Incidence of IHD (%)		Mortality from IHD (%)	
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In a recent Lipid Clinic….

74 year old male
Had participated in the 100,000 genomes project
Had been found to have an FH causing genetic variant

No history of any atherosclerotic cardiovascular disease

In 1980s, posted to work with the EEC in Brussels
Health screening – total cholesterol > 300 mg/dL (7.8 mM)
Doctor diagnosed FH based on this and his family history
Started taking a statin

Currently taking Atorvastatin 40 mg with LDL-C of 3.9 mM

FH: summary so far

Familial Hypercholesterolaemia is:

- A significant cause of premature cardiovascular disease and death
- Quite common
- Eminently treatable

FH: summary so far

Familial Hypercholesterolaemia is:

- A significant cause of premature cardiovascular disease and death
- Quite common
- Eminently treatable

So how can we do better at diagnosing it?

Diagnosing FH: Total Cholesterol

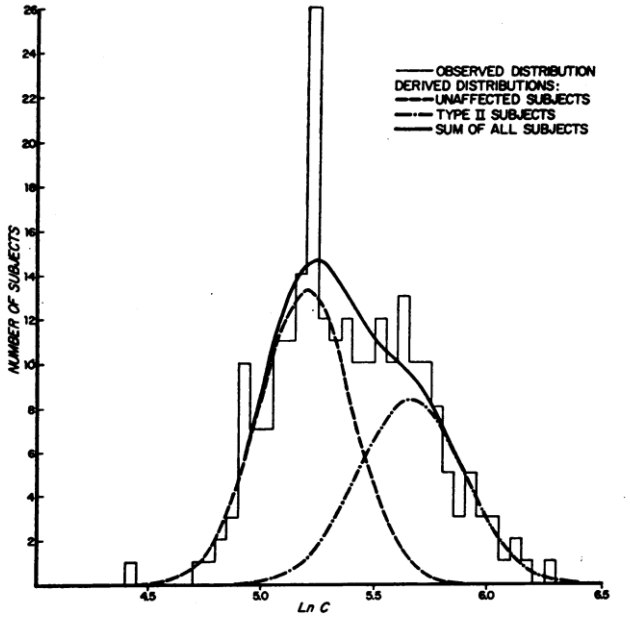


FIGURE 2 Distribution of cholesterol in the children. The natural logarithm (ln) of the plasma cholesterol (C) from 236 children is plotted on the abscissa. The observed distribution suggests bimodality and two populations are derived by a maximum likelihood method (17). The degree of overlap is sufficiently great so that the sum of the two populations is not bimodel but bitangential (see Results). The antimode for C is 235 mg/100 ml. 8.5% of the children in the normal (left) population were above the cutpoint (false positives) and 18.9% of the children in the affected (right) population were below the cutpoint (false negatives).

From Kwiterovich et al. J Clin Invest 1974;53:1237

Diagnosing FH: LDL Cholesterol

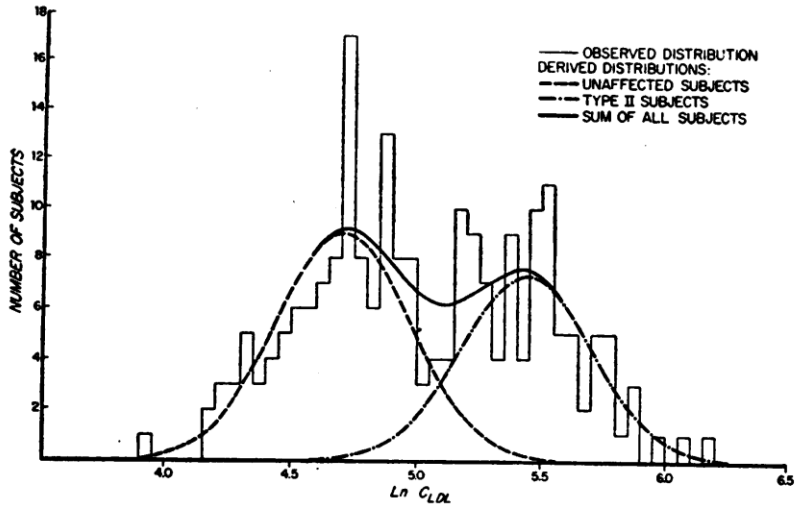


FIGURE 1 Distribution of low density lipoprotein cholesterol in the children. The natural logarithm (ln) of the low density lipoprotein cholesterol (C_{LDL}) from 217 children is plotted on the abscissa. The observed distribution appears bimodal and two populations are derived by the maximum likelihood method (17). The sum of the two derived distributions is bimodal. The antimode is a C_{LDL} of 164 mg/100 ml and 55% of the observations are in the left distribution. 7.2% of the children in the normal (left) population were above the cutpoint (false positives) and 9.7% of those in the affected (right) population were below the cutpoint (false negatives).

From Kwiterovich et al. J Clin Invest 1974;53:1237

Diagnosing FH: LDL Cholesterol

Even worse in adults

From NHANES III 15% of US men aged 45-54 have an LDL-C ≥ 4.9 mmol/L

Let's take 1000 men – 150 will have an LDL-C ≥ 4.9

Assume all HeFH have an LDL-C ≥ 4.9 and a population prevalence of 1 in 250, then 4 of those will have FH, and 146 will not.

FH risk estimation tools

Diagnosing FH: Simon Broome

- Definite Familial Hypercholesterolaemia
  - LDL-C ≥ 4.9 mM (≥ 16) or LDL-C ≥ 4.0 mM (<16)
    (or TC ≥ 7.5 in an adult or 6.7 in a child), plus
  - Tendon xanthomas in patient or relative, or presence of an FH causing genetic variant

- Possible Familial Hypercholesterolaemia
  - LDL-C ≥ 4.9 mM (≥ 16) or LDL-C ≥ 4.0 mM (<16)
    (or TC ≥ 7.5 in an adult or 6.7 in a child), plus
  - FH of MI < 60 (1º relative) or < 50 (2º relative), or LDL-C ≥ 4.9 mM or TC ≥ 7.5 mM in 1º or 2º relative

Diagnosing FH: Dutch Lipid Clinic (1)

- Family History
  - Premature ASCVD (1º male < 55, 1º female < 60) 1
  - 1º relative with LDL-C > 95th percentile or with tendon xanthomas or corneal arcus 2
- Clinical History
  - Premature CHD (male < 55, female < 60) 2
  - Premature CeVD or PAD (male < 55, female < 60) 1
- Examination
  - Tendon xanthoma 6
  - Corneal arcus before 45 4

Diagnosing FH: Dutch Lipid Clinic (2)

- LDL cholesterol levels
  - ≥ 8.5 mM 8
  - 6.5 – 8.4 mM 5
  - 5.0 – 6.4 mM 3
  - 4.0 – 4.9 mM 1
- DNA – functional FH causing genetic variant 8
- Total score
  - ≥ 8 definite FH, 6-8 probable FH, 3-5 possible FH

So can genetics help?

Familial Hypercholesterolaemia Genetic Testing

East Genomic Laboratory Hub

Part XII. Lipids

R134 Familial hypercholesterolaemia

Testing Criteria

Dutch (or Welsh) lipid clinic score >5, OR

Simon Broome criteria indicate possible FH (following assessment in a specialist Lipid Clinic or Familial Hypercholesterolaemia service)

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

Where in Pathway

At presentation

Requesting Specialties

- Cardiology
- Chemical Pathology
- Clinical Genetics
- Metabolic Medicine
- Paediatrics

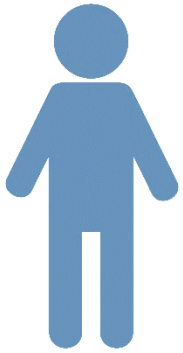
Specialist Service Group

- Core

Associated Tests

Please note all the tests below will be undertaken for R134 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R134.1	Familial hypercholesterolaemia Small panel	Singleton	Small variants	Panel of genes or loci	Familial hypercholesterolaemia – targeted panel (772)	Small panel
R134.2	LDLR MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	LDLR	MLPA or equivalent



R134 Familial Hypercholesterolaemia Diagnostic Testing

Screen for small variants and copy number variants in 5 genes

LDLR

LDLRAP1

PCSK9

APOB

APOE

Familial Hypercholesterolaemia Genetic Testing

East Genomic Laboratory Hub

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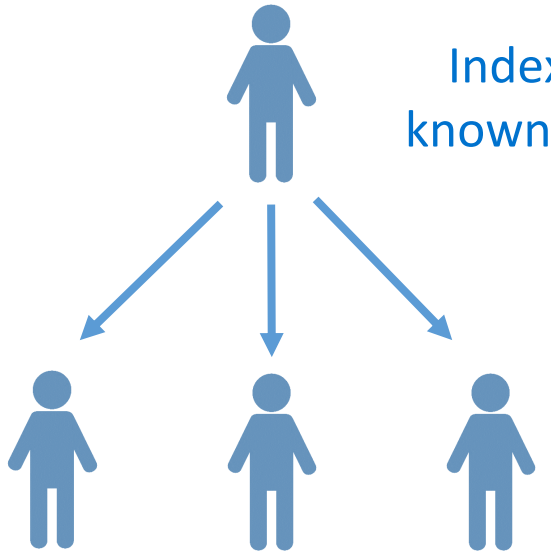


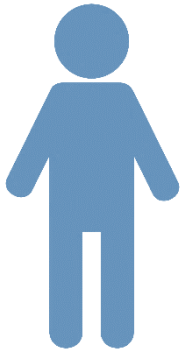
Index patient with known genetic variant

Familial Hypercholesterolaemia Cascade Testing

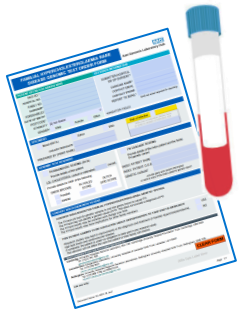
Presence or absence of known genetic variant in family

Familial Hypercholesterolaemia Genetic Testing

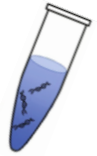
East Genomic Laboratory Hub



Patient Eligible?
Consent Discussion
Order Testing



Sample Receipt



DNA extraction

NGS Sequencing
LDLR
LDLRAP1
PCSK9
APOB
APOE

Bioinformatics

Analysis and Interpretation

Clinical Reporting

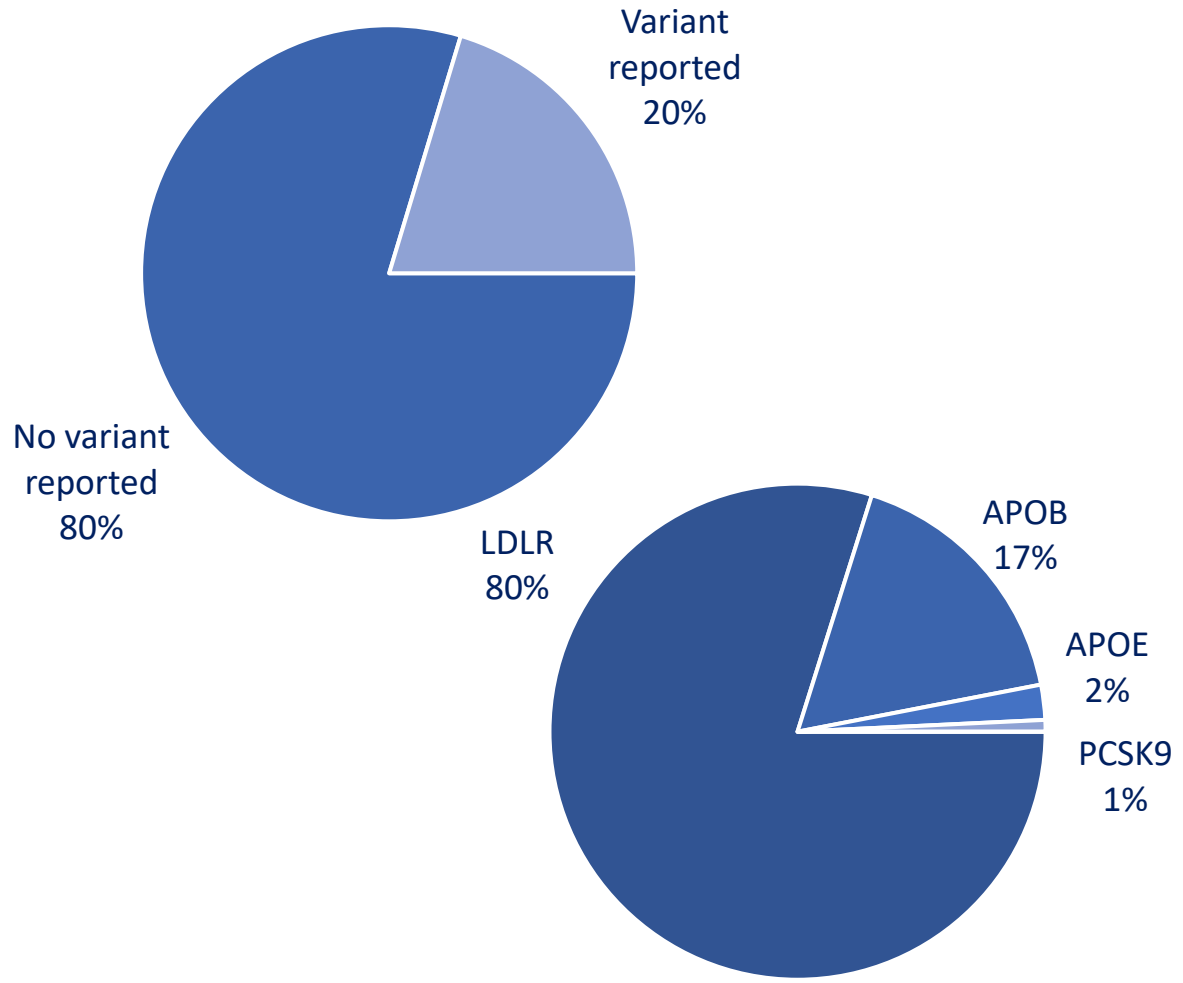
Familial Hypercholesterolaemia Genetic Testing

East Genomic Laboratory Hub

East GLH Diagnostic Yield

20% of diagnostic tests identify a pathogenic or likely pathogenic variant

National audit in 2021 indicated a 20% diagnostic yield

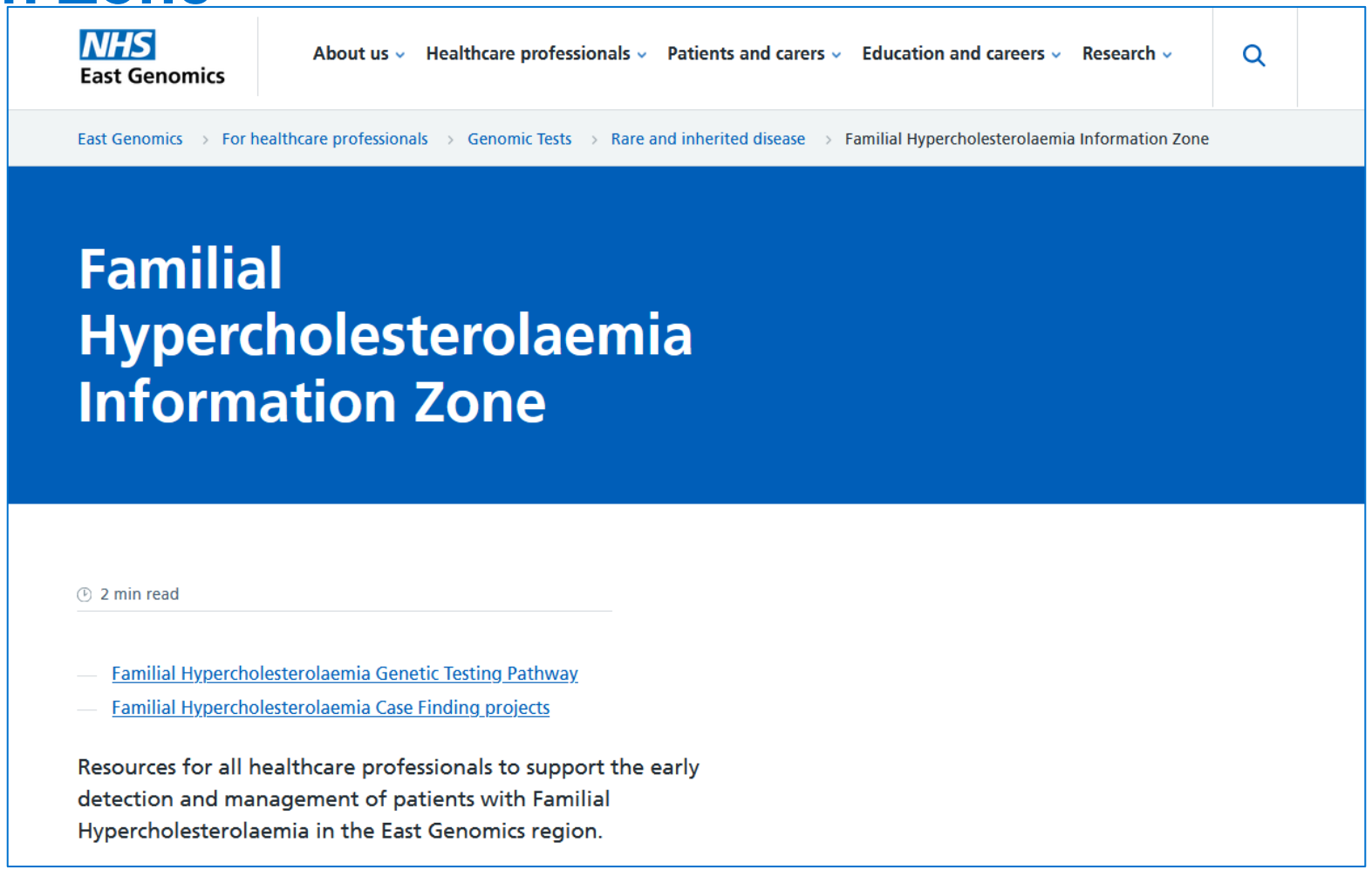


How you can help us retain this yield:

- identify appropriate patients for testing
- provide genomics team with good quality information on test order forms

Familial Hypercholesterolaemia Information Zone

East Genomic Laboratory Hub

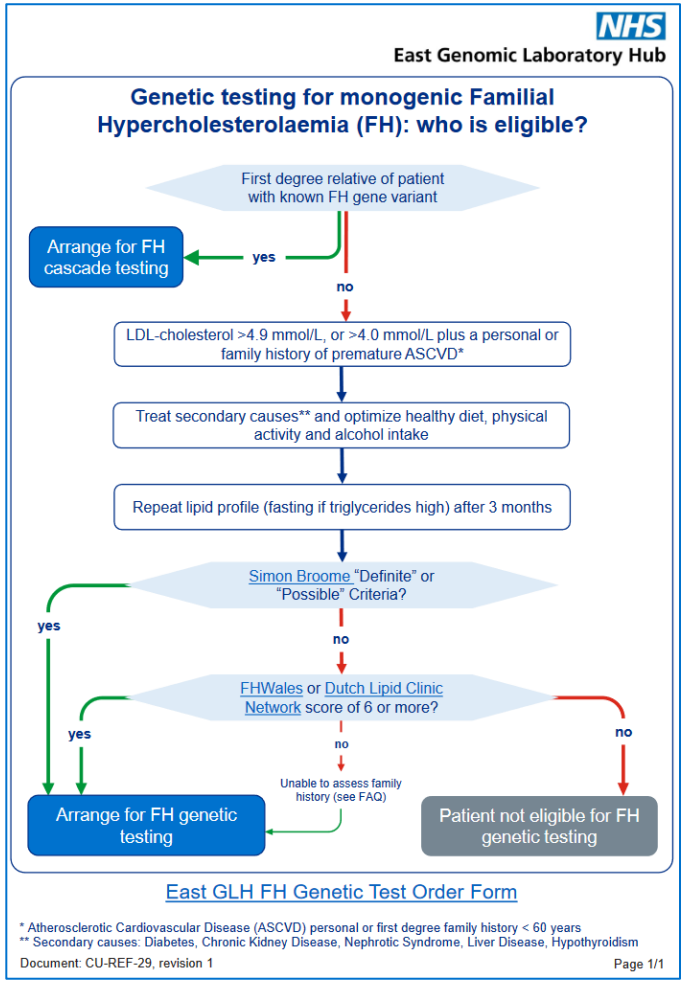


https://www.eastgenomics.nhs.uk/for-healthcare-professionals/genomic-tests/rare-and-inherited-diseases/familial-hypercholesterolaemia-information-zone/

Familial Hypercholesterolaemia Information Zone

East Genomic Laboratory Hub

FH Pathway



NHS East Genomic Laboratory Hub

Genetic testing for monogenic Familial Hypercholesterolaemia (FH): who is eligible?

First degree relative of patient with known FH gene variant

yes → Arrange for FH cascade testing

no

LDL-cholesterol >4.9 mmol/L, or >4.0 mmol/L plus a personal or family history of premature ASCVD*

Treat secondary causes** and optimize healthy diet, physical activity and alcohol intake

Repeat lipid profile (fasting if triglycerides high) after 3 months

Simon Broome "Definite" or "Possible" Criteria?

yes → Arrange for FH genetic testing

no

FHWales or Dutch Lipid Clinic Network score of 6 or more?

yes → Arrange for FH genetic testing

no → Unable to assess family history (see FAQ) → Arrange for FH genetic testing

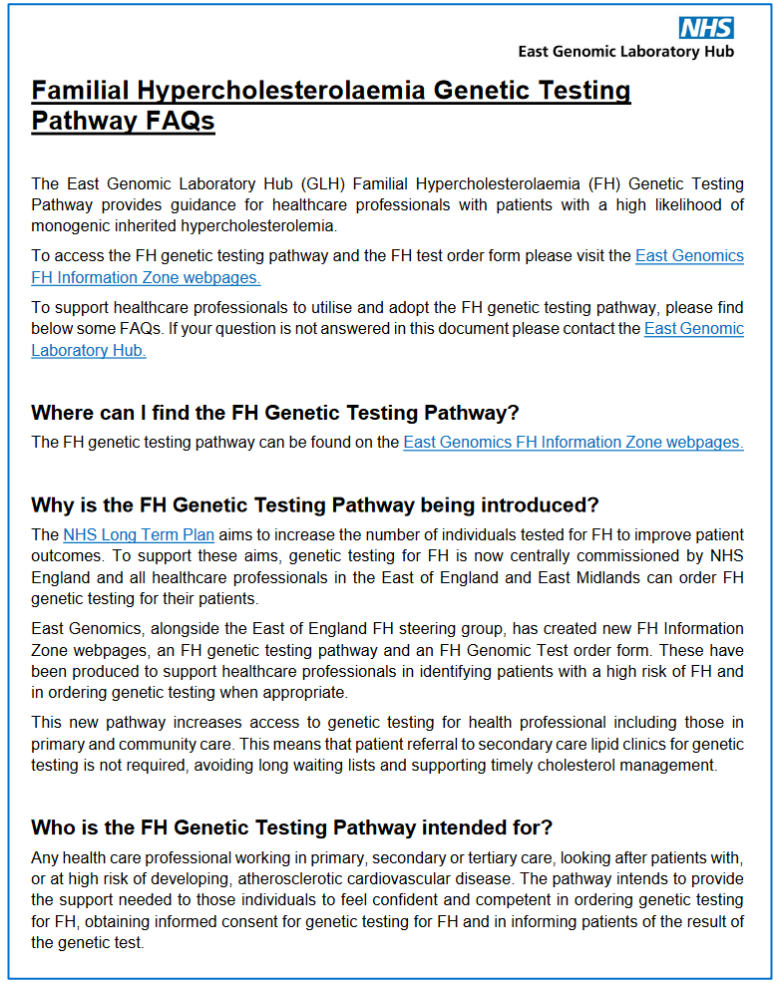
no → Patient not eligible for FH genetic testing

East GLH FH Genetic Test Order Form

* Atherosclerotic Cardiovascular Disease (ASCVD) personal or first degree family history < 60 years
** Secondary causes: Diabetes, Chronic Kidney Disease, Nephrotic Syndrome, Liver Disease, Hypothyroidism

Document: CU-REF-29, revision 1 Page 1/1

FH Pathway FAQs



NHS East Genomic Laboratory Hub

Familial Hypercholesterolaemia Genetic Testing Pathway FAQs

The East Genomic Laboratory Hub (GLH) Familial Hypercholesterolaemia (FH) Genetic Testing Pathway provides guidance for healthcare professionals with patients with a high likelihood of monogenic inherited hypercholesterolemia.

To access the FH genetic testing pathway and the FH test order form please visit the East Genomics FH Information Zone webpages.

To support healthcare professionals to utilise and adopt the FH genetic testing pathway, please find below some FAQs. If your question is not answered in this document please contact the East Genomic Laboratory Hub.

Where can I find the FH Genetic Testing Pathway?

The FH genetic testing pathway can be found on the East Genomics FH Information Zone webpages.

Why is the FH Genetic Testing Pathway being introduced?

The NHS Long Term Plan aims to increase the number of individuals tested for FH to improve patient outcomes. To support these aims, genetic testing for FH is now centrally commissioned by NHS England and all healthcare professionals in the East of England and East Midlands can order FH genetic testing for their patients.

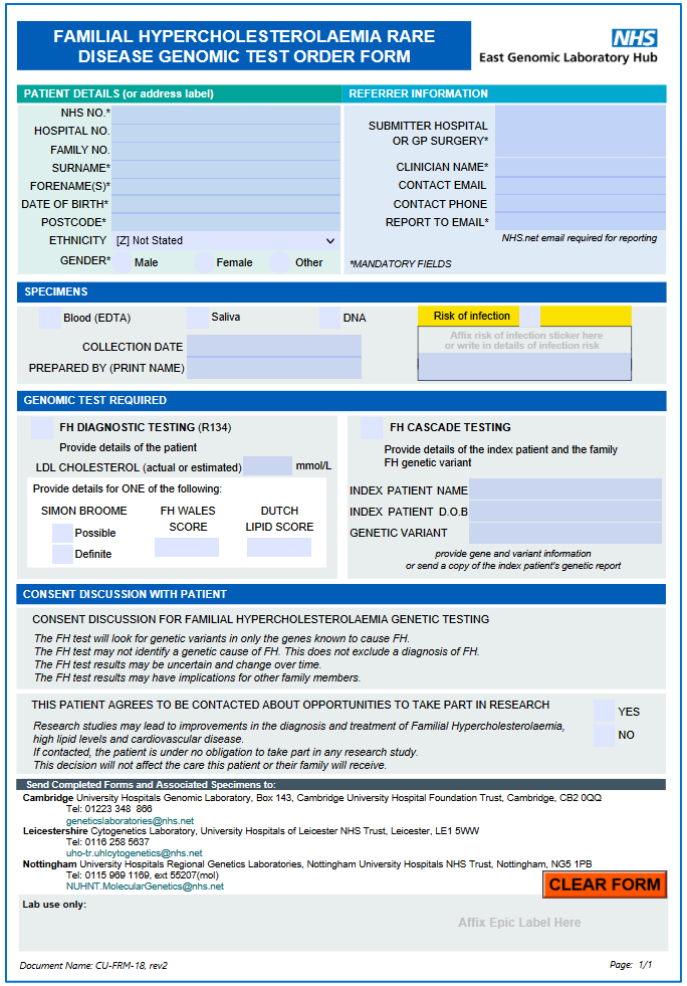
East Genomics, alongside the East of England FH steering group, has created new FH Information Zone webpages, an FH genetic testing pathway and an FH Genomic Test order form. These have been produced to support healthcare professionals in identifying patients with a high risk of FH and in ordering genetic testing when appropriate.

This new pathway increases access to genetic testing for health professional including those in primary and community care. This means that patient referral to secondary care lipid clinics for genetic testing is not required, avoiding long waiting lists and supporting timely cholesterol management.

Who is the FH Genetic Testing Pathway intended for?

Any health care professional working in primary, secondary or tertiary care, looking after patients with, or at high risk of developing, atherosclerotic cardiovascular disease. The pathway intends to provide the support needed to those individuals to feel confident and competent in ordering genetic testing for FH, obtaining informed consent for genetic testing for FH and in informing patients of the result of the genetic test.

FH Test Order Form



FAMILIAL HYPERCHOLESTEROLAEMIA RARE DISEASE GENOMIC TEST ORDER FORM

NHS East Genomic Laboratory Hub

PATIENT DETAILS (or address label)

NHS NO.* | HOSPITAL NO. | FAMILY NO. | SURNAME* | FORENAME(S)* | DATE OF BIRTH* | POSTCODE* | ETHNICITY [Z] Not Stated | GENDER* Male Female Other

REFERRER INFORMATION

SUBMITTER HOSPITAL OR GP SURGERY* | CLINICIAN NAME* | CONTACT EMAIL | CONTACT PHONE | REPORT TO EMAIL*

NHS.net email required for reporting

*MANDATORY FIELDS

SPECIMENS

Blood (EDTA) Saliva DNA

COLLECTION DATE | PREPARED BY (PRINT NAME)

Risk of infection

Affix risk of infection sticker here or write in details of infection risk

GENOMIC TEST REQUIRED

FH DIAGNOSTIC TESTING (R134)

Provide details of the patient

LDL CHOLESTEROL (actual or estimated) mmol/L

Provide details for ONE of the following:

SIMON BROOME: Possible / Definite | FH WALES SCORE | DUTCH LIPID SCORE

FH CASCADE TESTING

Provide details of the index patient and the family FH genetic variant

INDEX PATIENT NAME | INDEX PATIENT D.O.B | GENETIC VARIANT

provide gene and variant information or send a copy of the index patient's genetic report

CONSENT DISCUSSION WITH PATIENT

CONSENT DISCUSSION FOR FAMILIAL HYPERCHOLESTEROLAEMIA GENETIC TESTING

The FH test will look for genetic variants in only the genes known to cause FH.
The FH test may not identify a genetic cause of FH. This does not exclude a diagnosis of FH.
The FH test results may be uncertain and change over time.
The FH test results may have implications for other family members.

THIS PATIENT AGREES TO BE CONTACTED ABOUT OPPORTUNITIES TO TAKE PART IN RESEARCH — YES / NO

Research studies may lead to improvements in the diagnosis and treatment of Familial Hypercholesterolaemia, high lipid levels and cardiovascular disease.
If contacted, the patient is under no obligation to take part in any research study.
This decision will not affect the care this patient or their family will receive.

Send Completed Forms and Associated Specimens to:

Cambridge University Hospitals Genomic Laboratory, Box 143, Cambridge University Hospital Foundation Trust, Cambridge, CB2 0QQ
Tel: 01223 348 866
genetics!laboratories@nhs.net

Leicestershire Cytogenetics Laboratory, University Hospitals of Leicester NHS Trust, Leicester, LE1 5WW
Tel: 0116 258 5637
uho-tr.uhlcytogenetics@nhs.net

Nottingham University Hospitals Regional Genetics Laboratories, Nottingham University Hospitals NHS Trust, Nottingham, NG5 1PB
Tel: 0115 969 1169, ext 55207(mol)
NUHNT.MolecularGenetics@nhs.net

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Lab use only:

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Familial Hypercholesterolaemia Consent

East Genomic Laboratory Hub

- Aim to ensure you are competent and confident to discuss genomic testing with your patient
- Aim to make the consent conversation proportional to genomic test

CONSENT DISCUSSION WITH PATIENT

CONSENT DISCUSSION FOR FAMILIAL HYPERCHOLESTEROLAEMIA GENETIC TESTING

The FH test will look for genetic variants in only the genes known to cause FH.
The FH test may not identify a genetic cause of FH. This does not exclude a diagnosis of FH.
The FH test results may be uncertain and change over time.
The FH test results may have implications for other family members.

THIS PATIENT AGREES TO BE CONTACTED ABOUT OPPORTUNITIES TO TAKE PART IN RESEARCH

☐ YES
☐ NO

Research studies may lead to improvements in the diagnosis and treatment of Familial Hypercholesterolaemia, high lipid levels and cardiovascular disease.
If contacted, the patient is under no obligation to take part in any research study.
This decision will not affect the care this patient or their family will receive.

FHWales criteria

https://fhwalescriteria.co.uk

Eligibility for FH genetic testing

Proband

1. Simon Broome criteria met
2. DLCN or Age adjusted FHWales score more than 5 (≥ 6)
3. Special circumstances, usually where family history cannot be fully ascertained

Cascade

First degree relative of anyone with a proven FH causing genetic variation

Diagnosing FH: FamCat2

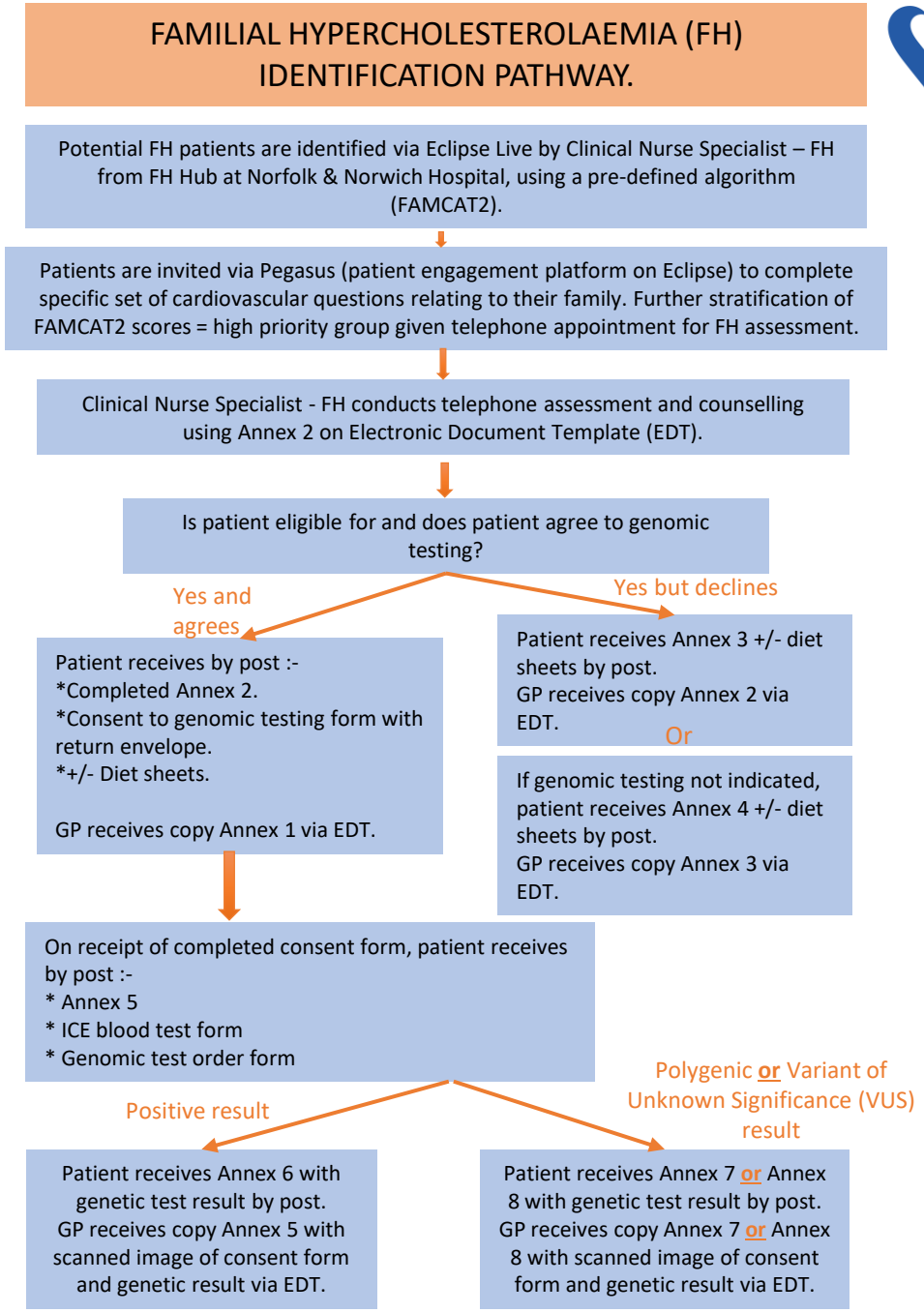
- x4 positive predictive value than Simon Broome:
  - Simon Broome: 10.3%
  - FamCat2: 43.4%

- Simon Broome: detection rate 11.3%
- DLCN (score >6): detection rate 35%
- FamCat2: detection rate 50%

Qureshi et al. Comparing the performance of the novel FAMCAT algorithms and established case-finding criteria for familial hypercholesterolaemia in primary care. BMJ 2021

FH identification Pilot program in Norfolk:

- Approved by N&W ICB and NNUH.
- Agreed by LMC.
- Supported by East GMSA and Health. Innovation East.
- Embedded in Eclipse.
- Based on FamCat2 risk calculation.
- Run by secondary care team, with FH specialist nurse.



Tackling Cholesterol Together

HEART UK THE CHOLESTEROL CHARITY

NHS

What does it imply?

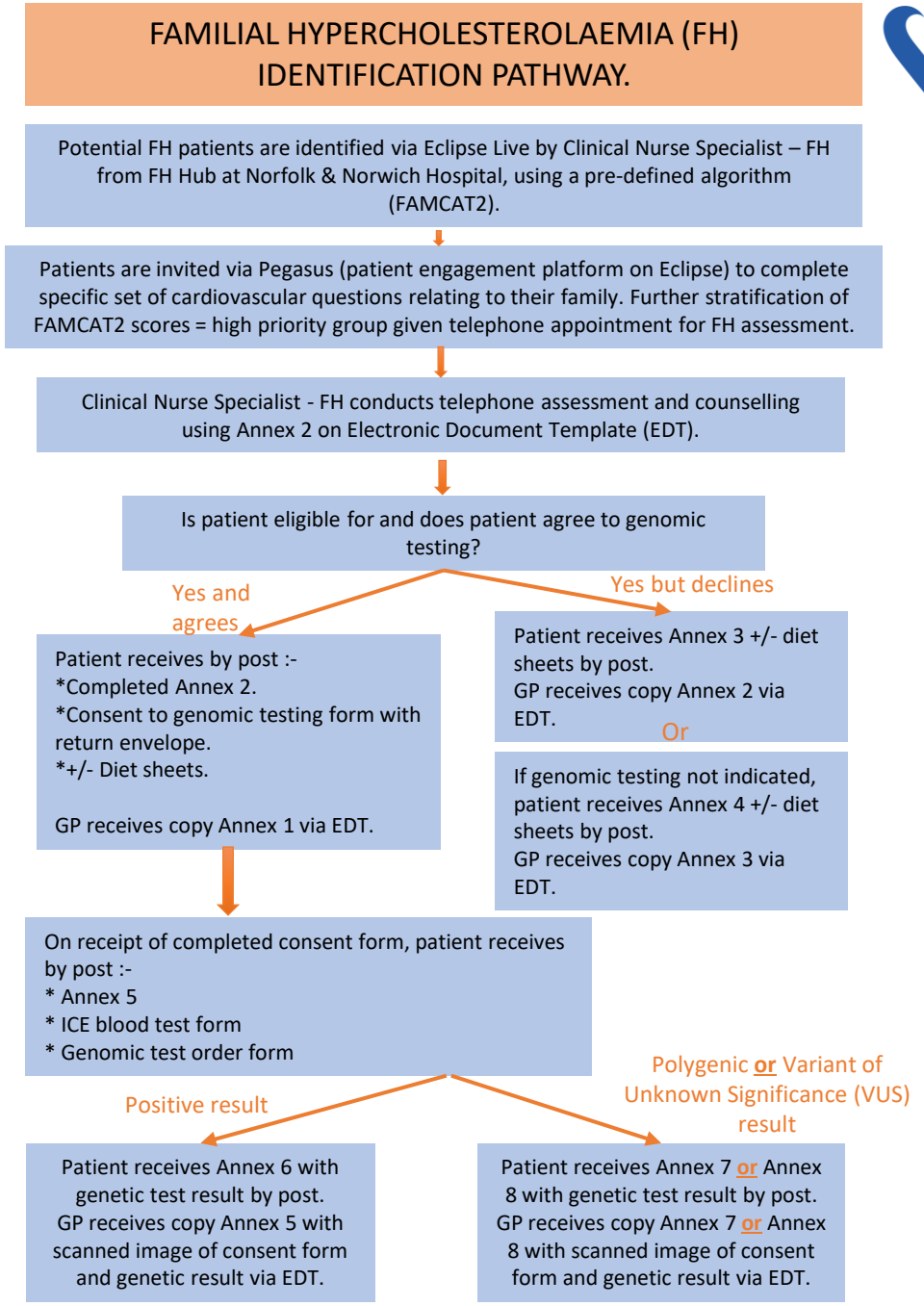
- Appointments, correspondence with patients, letters, genetics testing, results follow up – all done by secondary care team in behalf of primary care.

What does it require?

- "Proforma" submitted by Surgeries in order to be included in the project – simple agreement digital form.

Outcomes in the few weeks it has been live:

- More that 100 patients fully screened, from >30 surgeries.



East Genomics FH Testing Pathway

https://www.eastgenomics.nhs.uk

Search ‘FH’

Tackling Cholesterol Together

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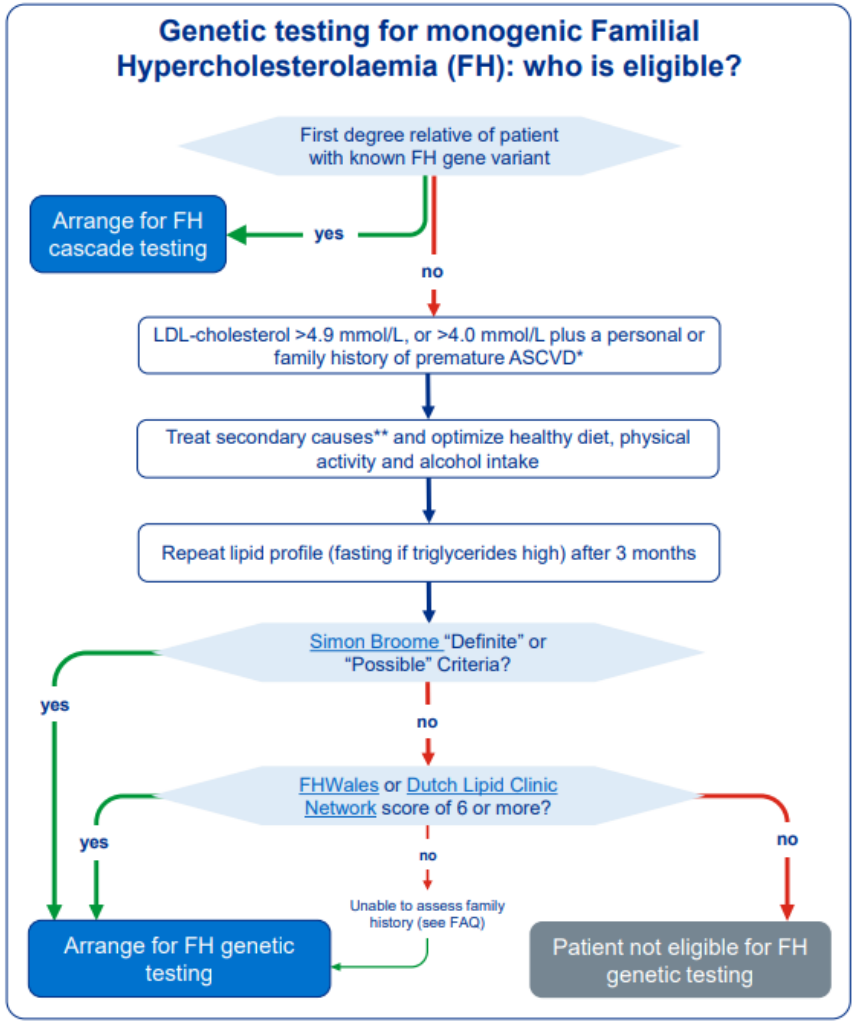
Genetic testing for monogenic Familial Hypercholesterolaemia (FH): who is eligible?



East GLH FH Genetic Test Order Form

* Atherosclerotic Cardiovascular Disease (ASCVD) personal or first degree family history < 60 years
** Secondary causes: Diabetes, Chronic Kidney Disease, Nephrotic Syndrome, Liver Disease, Hypothyroidism

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Lowering Cholesterol.

Saving Lives.

Tackling Cholesterol Together

Thank you
Any questions?

ICB and/or another organisation logo/s to go here (if using)