Lowering Cholesterol.

Saving Lives.

Tackling Cholesterol Together

A Focus on Familial Hypercholesterolaemia (FH)

Welcome to the fourth in a series of webinars as part of the national education programme Tackling Cholesterol Together.

Delivered in partnership by The NHS Accelerated Access Collaborative (AAC), The AHSN Network and the cholesterol charity, HEART UK

The webinar will start at 1pm

October 2021

All programme content, recordings and next webinar and clinic bookings will be housed in the HEART UK pages. Visit the site for the **new** e-Learning modules on Identifying FH in primary care, the Lipid Management Pathway and Statin Intolerance https://www.heartuk.org.uk/tackling-cholesterol-together/home

This campaign is being funded by Novartis Pharmaceuticals UK Ltd. as part of a collaborative working agreement for lipid management, with NHS England & Improvement (NHSE&I) and Accelerated Access Collaborative (AAC). Novartis, NHSEI& and AAC contribute resources in the form of skills, expertise, project management and administrative activity. Novartis has approved the associated materials in line with the ABPI Code.

TheAHSNNetwork

ACCELERATED ACCESS COLLABORATIVE

HEART UK THE CHOLESTEROL CHARITY

NHS

NOVARTIS

Housekeeping

- **This meeting will be recorded** and will be made available in the HEART UK Tackling Cholesterol Together pages
- **There will be time** to stop and ask questions at the end of each section
- **Feel free to ask questions** or upvote questions in the chat function when it becomes available
- **Any questions that we are not able to cover in the Q&A** sections today will be addressed following the event
- **Any questions you provided** during registration will be covered during the session

Agenda

	Topic	Presenter
01	**Webinar objectives. Management of CVD burden as a holistic approach**	Sue Critchley
02	**Genetics and diagnosis of FH**	Dr Mahtab Sharifi
03	**Management of FH**	Dr Jai Cegla
04	**Identification of FH cases in primary care**	Professor Nadeem Qureshi
05	**Close and next steps**	Sue Critchley

Objectives of today's Webinar

01

Learn about the genetic causes of FH and the FH register criteria. **Appreciate** the mortality risk and lifetime LDL-C burden in FH for men and women

02

Introduction to the LDL receptor variants and the causal gene mutations. **Understand** the pathway on which NICE recommended novel therapies act

03

Know **how to look** for and **manage** FH. **Understand** why people with FH have such early coronary heart disease. **Appreciate** the treatment effect of NICE recommended novel therapies

04

See the systematic and opportunistic **case finding methods** in primary care, based on recommendations by NICE and the **FAMCAT** FH prediction model

CVD Burden Remains a Significant Unmet Need across all risk factors

CVD in the UK[1]

- >7 million people have CVD
- CVD has an annual total healthcare cost of £9 billion
- CVD is one of the biggest causes of death despite the availability of medical interventions and strategies

The NHS Long-Term Plan:[2]

Up to 10 year outlook for a variety of healthcare topics

- Cholesterol was highlighted for the first time in a decade
- CV risk management is a combined approach: ABC (AF, Blood pressure, Cholesterol)

167,000 deaths/year from CVD; **44,000** are premature[1]

Improve early detection and treatment of CVD
NHS Long-Term Plan[2]

>100,000 hospital admissions/year for an MI[1]
>100,000 strokes/year[1]

Prevent 150,000 heart attacks, strokes and dementia cases
NHS Long-Term Plan[2]

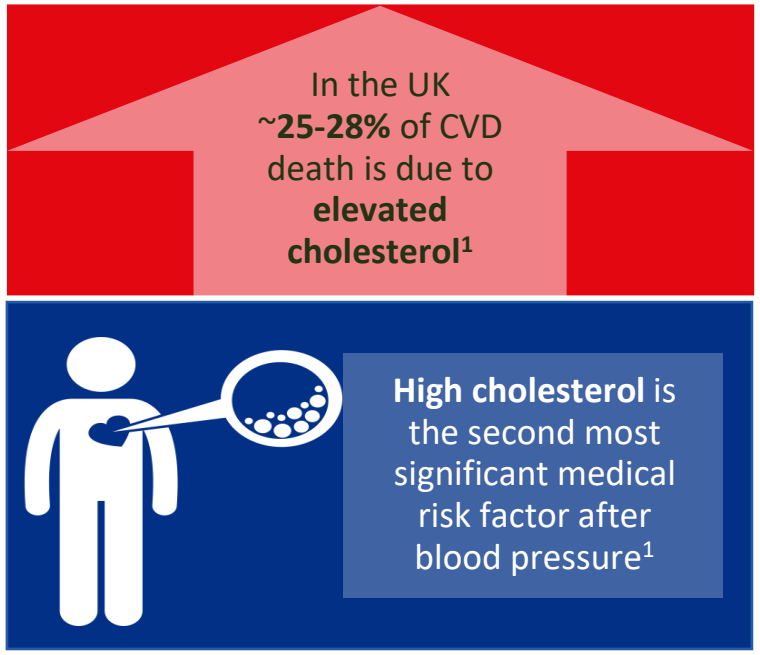
Up to **260,000** people in the UK have HeFH[3]

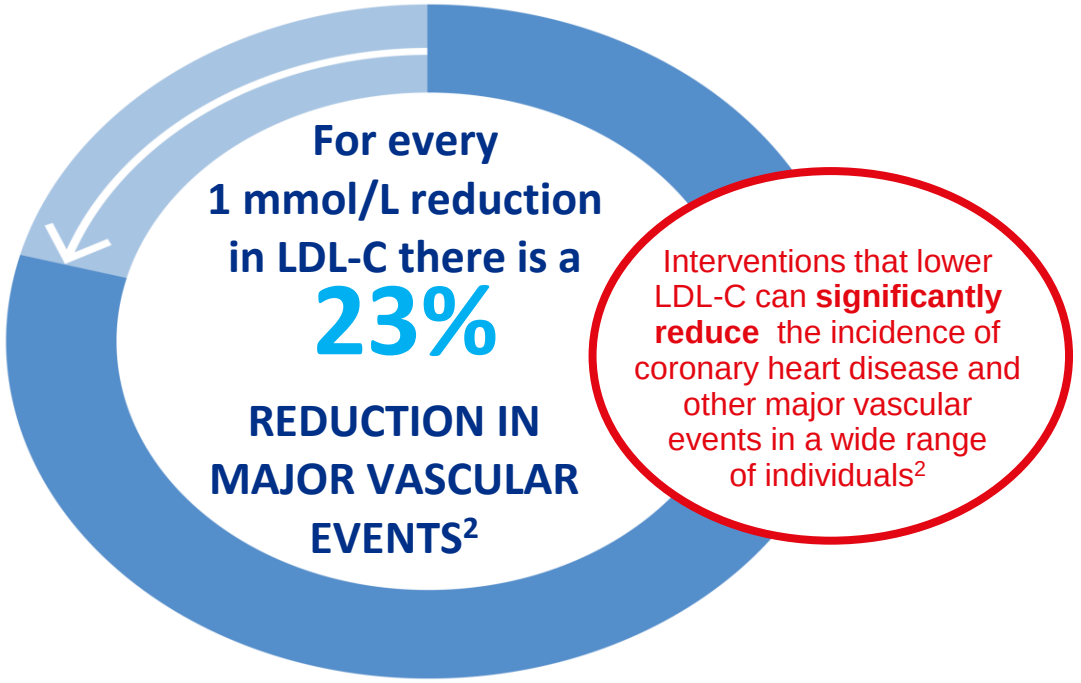
Expand access to genetic testing for identification of FH cases to at least 25% in 5 years
NHS Long-Term Plan[2]

- AF, atrial fibrillation; CV, cardiovascular; CVD, cardiovascular disease; FH, familial hypercholesterolaemia; HeFH, heterozygous familial hypercholesterolaemia; MI, myocardial infarction.

- 1. BHF. UK Factsheet, August 2019. Available at: https://www.bhf.org.uk/what-we-do/our-research/heart-statistics. Accessed November 2019;
  2. NHS Long-Term Plan. Available at: https://www.longtermplan.nhs.uk/wp-content/uploads/2019/08/nhs-long-term-plan-version-1.2.pdf;
  3. NICE Clinical Guidance [CG71]. Available at: https://www.nice.org.uk/guidance/cg71/. Accessed December 2019.

Why is cholesterol management so important in CVD prevention?





CVD, cardiovascular disease; LDL-C low density lipoprotein cholesterol

02

Genetics and diagnosis of FH

Dr Mahtab Sharifi
Consultant Chemical Pathologist, St Georges' Hospital NHS Trust

Genetic Causes of Familial Hypercholesterolaemia

Mahtab Sharifi- Consultant, St George's Hospital
Steve Humphries - Emeritus Professor Cardiovascular Genetics, UCL

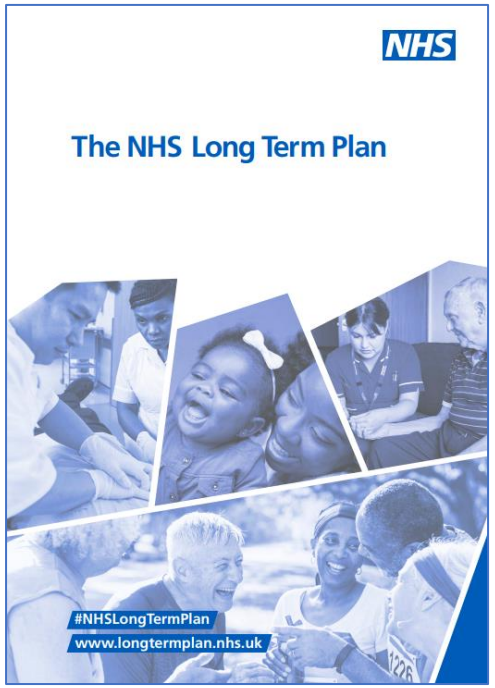
- **Diagnosis - Simon Broome and Dutch Score**
- ***LDLR/APOB/PCSK9/APOE* cause FH**
- **Polygenic FH**

CVG - Ros Whittall, Marta Futema*, Sarah Leigh, Ebele Usefo, Jackie Cooper, Philippa Talmud, Ruth Lovering*; UGI - Sonia Shah, Vincent Plagnol. Royal Free Lipid Clinic - Devi Nair*, Mahtab Sharifi; GOSH DNA Lab - Alison Taylor-Beading*; Bristol DNA Lab - Maggie Williams*; Simon Broome Study Group - Andrew Neil*, Nigel Capps*, Ian McDowell*, Handrean Soran*, Paul Durrington*; PASS - Kate Haralambos*

British Heart Foundation

The NHS Long Term Plan – Jan 2019

Currently only 7% of those with FH have been identified, but we will aim to improve that to at least 25% in the next five years through the NHS genomics programme.



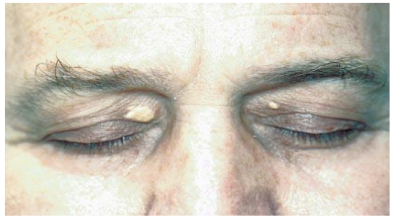
FH Diagnostic criteria

Simon Broome FH Register criteria:

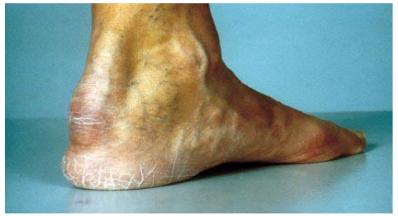
- Cholesterol > 7.5mmol/l or LDL > 4.9mmol/l in adult
- Cholesterol > 6.7mmol/l or LDL > 4.0mmol/l if < 16 yrs
- PLUS family history of high cholesterol or MI (<55yrsM)
- OR PLUS Tendon Xanthoma
- OR FH-causing mutation

Corneal Arcus

Xanthelasma



Tendon Xanthoma



Also Dutch Lipid Clinic Criteria scoring system & US system MEDPED

	Dutch Lipid Clinic Network Criteria	Points
Family history	1st-degree relative with known CVD (M <55yrs/F<60yrs)….	1
	1st-degree relative with TX and/or arcus	2
Clinical history	Patient with premature CHD	2
	Patient with premature stroke or PVD	1
Physical examination	Tendon xanthomata	6
	Arcus cornealis prior to age 45 years	4
LDL-C levels	LDL-C >=8.5	8
	LDL-C 6.5-8.4	5
	LDL-C 5.0-6.4	3
	LDL-C 4.0-4.9	1
DNA analysis	Functional mutation in the LDLR gene	8

>8 points = Definite FH
6 - 8 = Probable FH
3 - 5 = Possible FH

Welsh include –ve points for high TG – Haralambos et al 2014

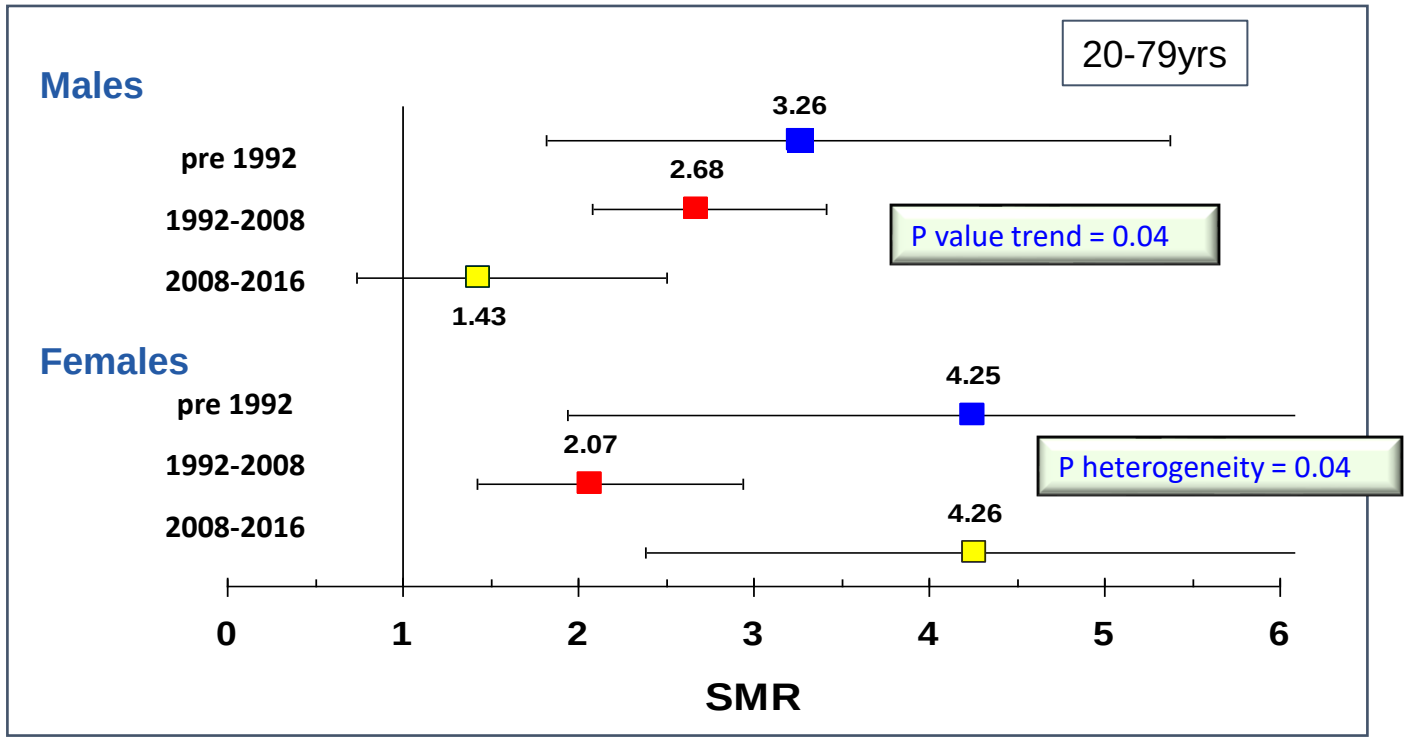
How high is CVD risk in untreated and treated Definite FH?

The UK "Simon Broome" FH Register

Use Simon Broome Register to

- **Compare Mortality Rate versus general population**
- **Look at 1980-1992 (lipid lowering by diet, resins)**
- **1992-2008 when FH patients were first to get statins**
- **After 2008 when high intensity statins became available**

SMR CHD Deaths for DFH Men vs Women over time

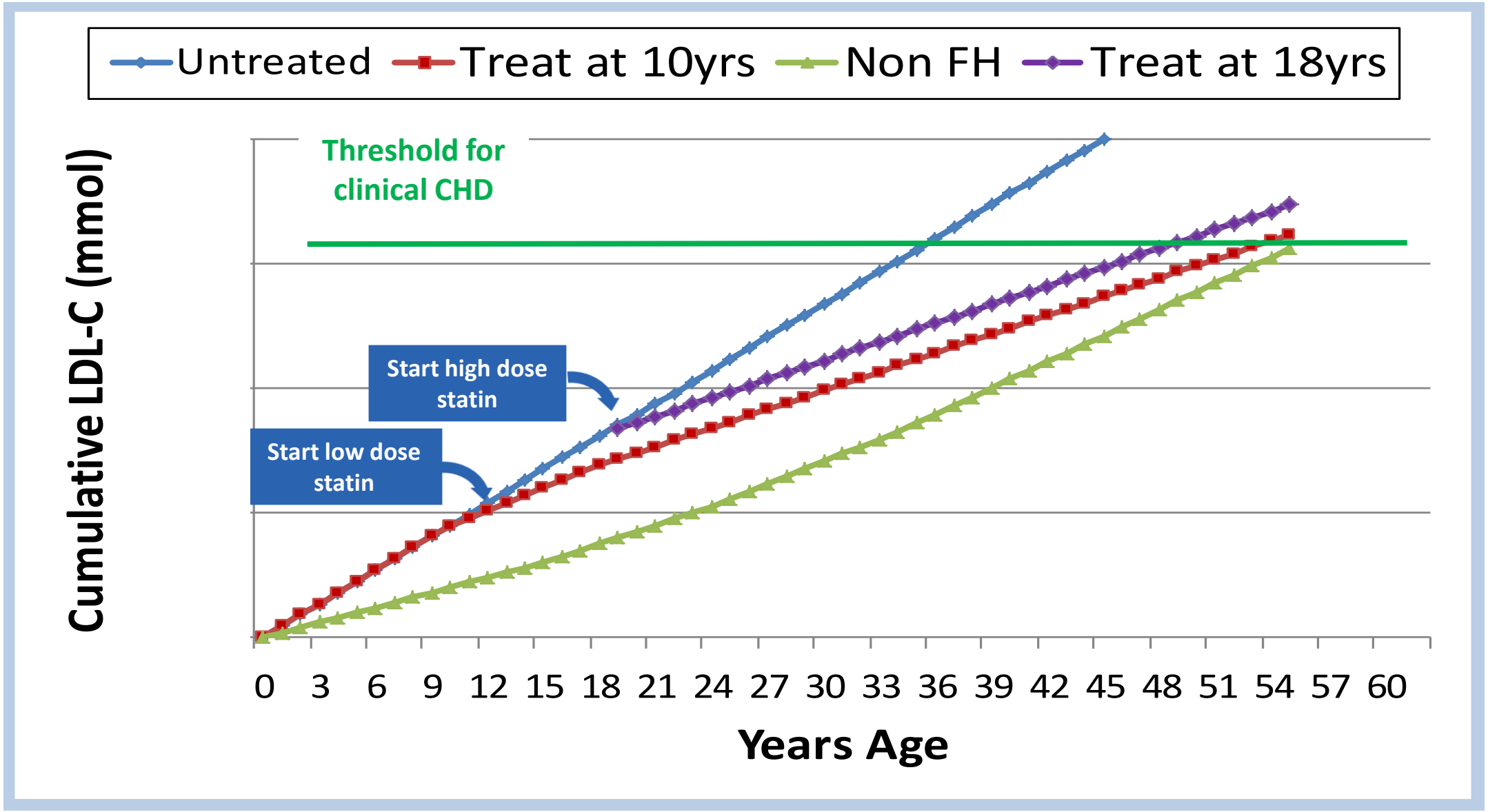


Over the three time periods CHD mortality falls progressively in men (SMR 56% lower) but not in women

Are women being treated later (post children)/with lower doses/lower potency statins?

Risk is so high in FH because of lifetime LDL-C Burden

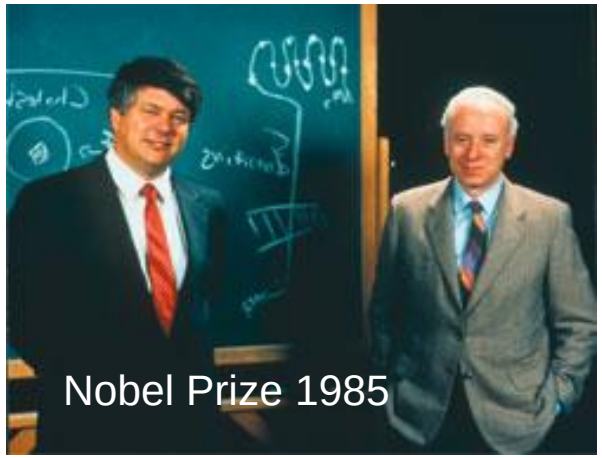
LDL "Burden" = ∑measured LDL-C x age

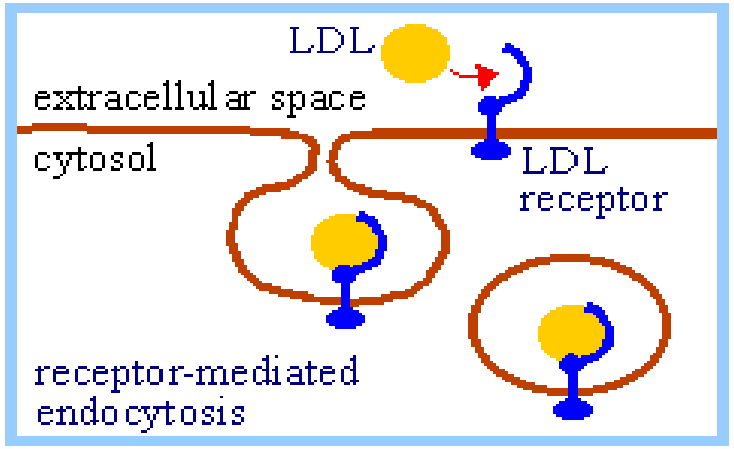


NICE recommends "Consider statin by age 10.." to reduce premature CHD burden

The Low Density Lipoprotein Receptor Gene

- FH due to defect in clearance of atherogenic LDL from blood → CHD
- Pioneering work from Mike Brown and Joe Goldstein and colleagues identified LDL-receptor as major cause





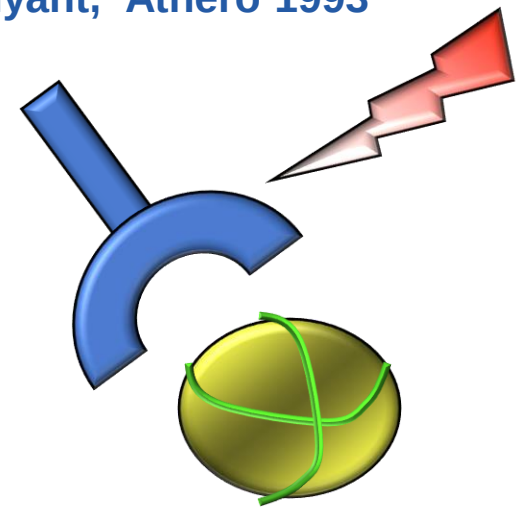
Lack of functional receptors on liver → fail to clear LDL from blood

Finding the genetic causes of FH → valuable insight into the cell biology and plasma handling of lipids and → development of novel therapies

More than 2300 different *LDLR* variants reported in FH patients world-wide – mis-sense, ins/dels, splice, promoter etc. Growing every day as more NGS done

Second FH Gene – APOB - Innerarity et al PNAS 1997

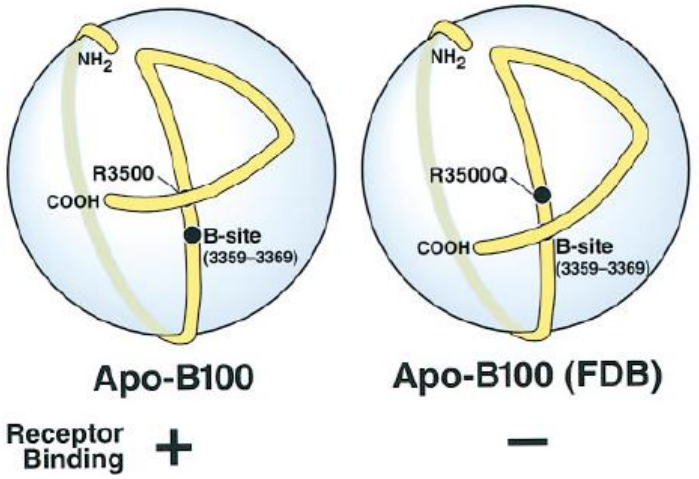
Myant, Athero 1993



Carriers of 3527Gln in UK
~ 1.2/1000

- Majority caused by single mutation in *APOB* gene
- Alters Arg3500 to Gln (R3500Q) (now p.R3527Q)
- Causes LDL to bind poorly to LDLR
- Leads to slower clearance and higher plasma LDL
- Milder than LDLR-FH but is expressed in childhood
- All patients “identical by descent” – mutation ~5000 years old

Cys disulphide 3167-3297



J Boren et al. *J Clin Invest.* (1998)

APOB R3527Q is most common cause of FH in UK

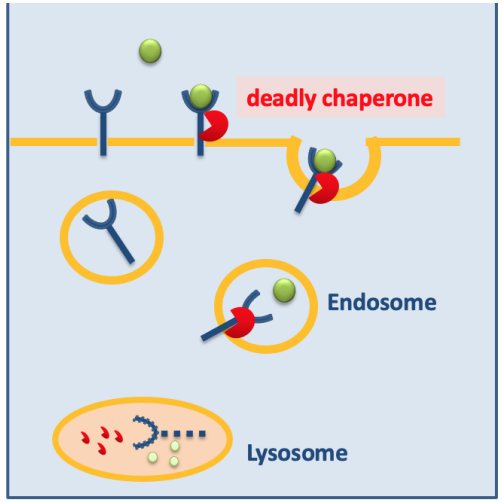
PCSK9 : the 15 year pathway

Mutations in *PCSK9* cause autosomal dominant hypercholesterolemia

Marianne Abifadel[1,2], Mathilde Varret[1], Jean-Pierre Rabès[1,3], Delphine Allard[1], Khadija Ouguerram[4], Martine Devillers[1], Corinne Cruaud[5], Suzanne Benjannet[6], Louise Wickham[6], Danièle Erlich[1], Aurélie Derré[1], Ludovic Villéger[1], Michel Farnier[7], Isabel Beucler[8], Eric Bruckert[9], Jean Chambaz[10], Bernard Chanu[11], Jean-Michel Lecerf[12], Gerald Luc[12], Philippe Moulin[13], Jean Weissenbach[5], Annick Prat[6], Michel Krempf[4], Claudine Junien[1,3], Nabil G Seidah[6] & Catherine Boileau[1,3]

Nature Genetics 2003

Gain of function → FH



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sequence Variations in *PCSK9*, Low LDL, and Protection against Coronary Heart Disease

Jonathan C. Cohen, Ph.D., Eric Boerwinkle, Ph.D., Thomas H. Mosley, Jr., Ph.D., and Helen H. Hobbs, M.D.

NEJM 2006

Loss of function → ↓LDL

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D., Anthony C. Keech, M.D., Narimon Honarpour, M.D., Ph.D., Stephen D. Wiviott, M.D., Sabina A. Murphy, M.P.H., Julia F. Kuder, M.A., Huei Wang, Ph.D., Thomas Liu, Ph.D., Scott M. Wasserman, M.D., Peter S. Sever, Ph.D., F.R.C.P., and Terje R. Pedersen, M.D., for the FOURIER Steering Committee and Investigators*

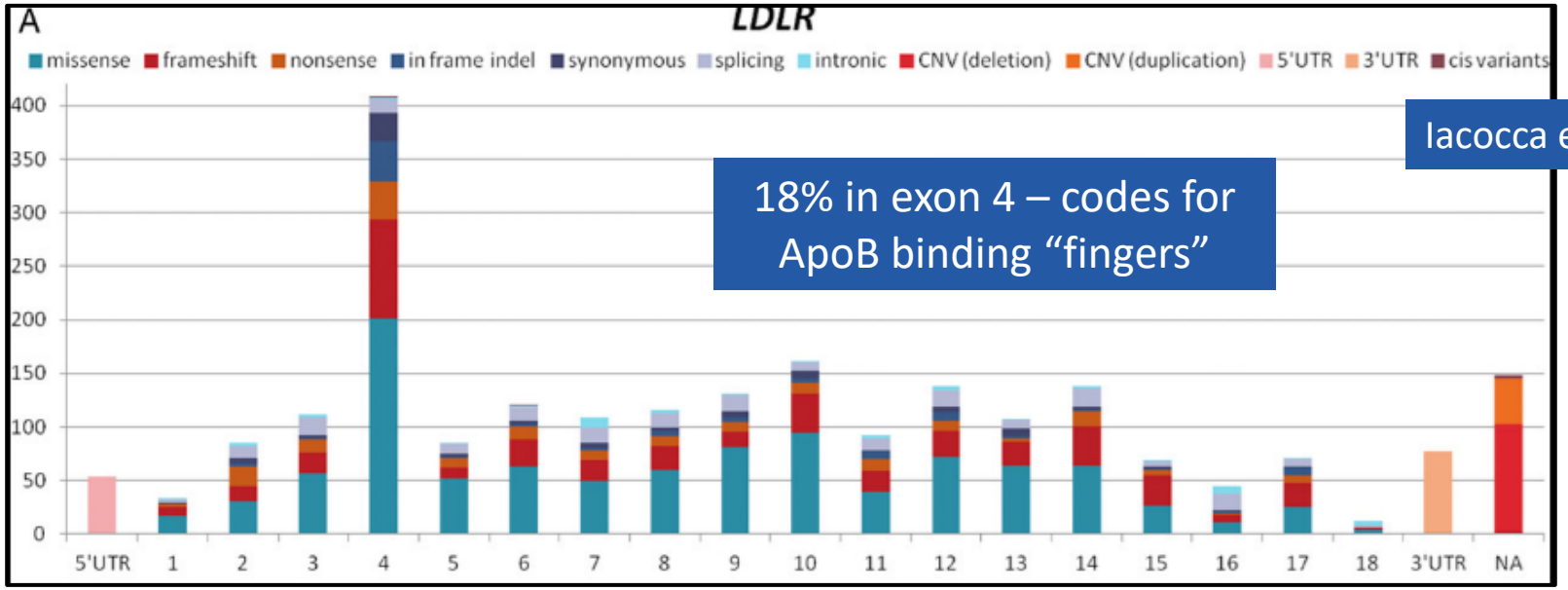
NEJM 2017

Reduces CHD events

Many gain-of-function (FH) and loss of function (protective) variants known.

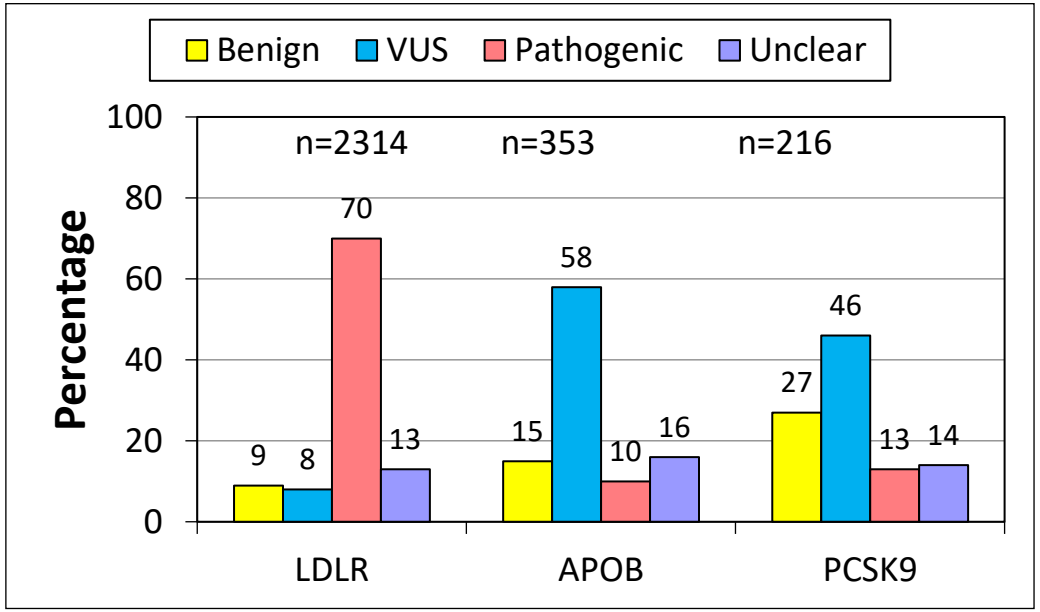
Only common FH-causing mutation in UK is D374Y - severe and penetrant at young age

Examination of published FH-causing variants



Iacocca et al Hum Mut 2018

18% in exon 4 – codes for ApoB binding "fingers"



Published variants "coded" using strict ACMG criteria

Only Pathogenic/likely pathogenic variants reported as FH-causing. All VUS need further work to → FH causing or not

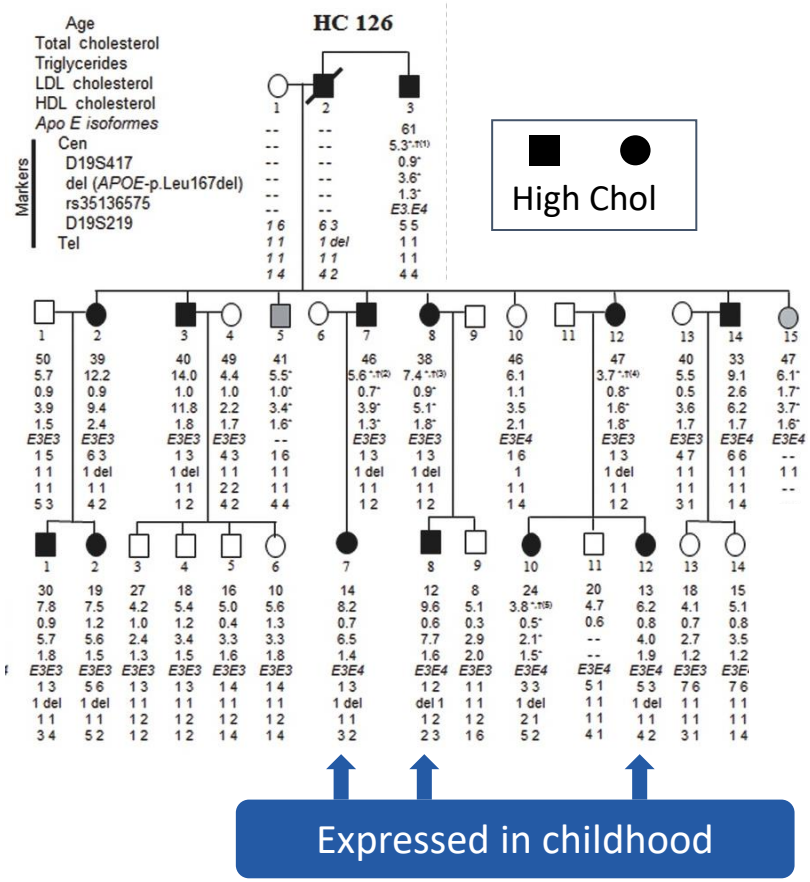
https://databases.lovd.nl/shared/genes/LDLR

4th Gene? - APOE p.Leu167del causes FH

Description of a Large Family with Autosomal Dominant Hypercholesterolemia Associated with the *APOE* p.Leu167del Mutation

Hum Mutat 34:83–87, 2013.

Marie Marduel,[1–3] Khadija Ouguerram,[4] Valérie Serre,[2,5] Dominique Bonnefont-Rousselot,[3,6,7] Alice Marques-Pinheiro,[2] Knut Erik Berge,[8] Martine Devillers,[2] Gérald Luc,[9,10] Jean-Michel Lecerf,[10] Laurent Tosolini,[1] Danièle Erlich,[5] Gina M. Peloso,[11] Nathan Stitziel,[11] Patrick Nitchké,[3,12] Jean-Philippe Jaïs,[3,12] The French Research Network on ADH,† Marianne Abifadel,[1,13] Sekar Kathiresan,[11] Trond Paul Leren,[8] Jean-Pierre Rabès,[1,14,15] Catherine Boileau,[1,14,15] and Mathilde Varret[1,5]*



- Genome-wide mapping+ exome sequencing
- Found 3bp deletion in *APOE* → p.(Leu167del)
- This de-stabilises α-helix in binding domain
- Demonstrated co-segregation with high LDL-C
- And decreased catabolism of LDL

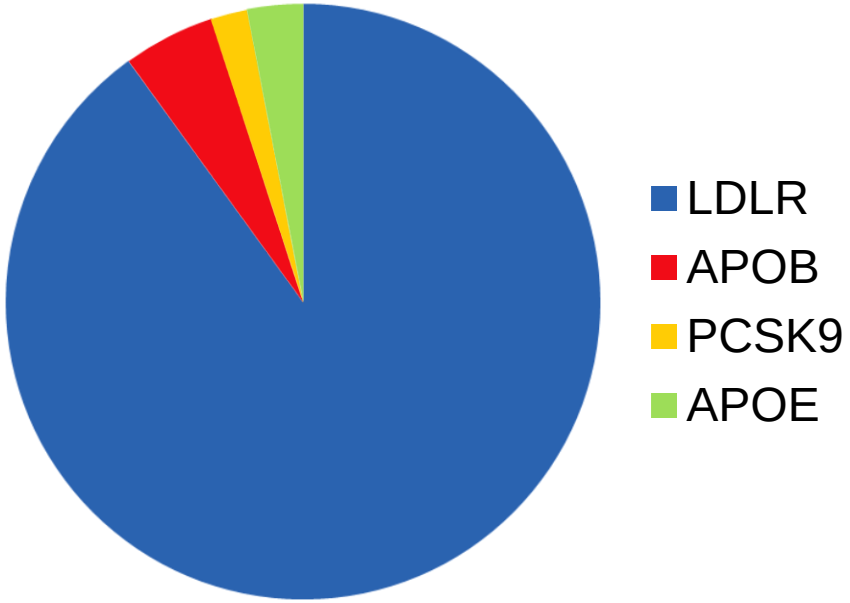
Confirmed by Cenarro et al 2016

- Sequenced *APOE* in 288 no mutation *LDLR/APOB/PCSK9* FH patients
- Found 3.1% carried p.(Leu167del), none in 220 control subjects
- Showed AD pattern in 8 families – LDL-C in carriers = 6.6mmol/l vs 3.7mmol/l in non carriers but Tg also mildly (50%) elevated

NGS panel for FH should include *APOE*

Genetic Causes of FH in UK

- ***LDLR*** **– Commonest cause >2300 world wide >400 in UK**
- ***APOB*** **– One common mutation p.R3527Q**
- ***PCSK9*** **– Gain of Function – Least frequent but most severe cause**
- ***APOE*** **– Leu167del freq unknown**
- ***LIPA*** **– Homozygosity → recessive FH**
- ***LDLRAP1*** **– homozygosity (stop)→ recessive FH**



DNA tests for FH - Offered by all 7 UK NHS Diagnostic Genomic Hub Labs

- **All use NGS to capture and sequence exons of all genes in one run**
- **96 samples can be handled in one run**
- **Costs fallen from £6-700 to ~£250, single mutation in relative ~ £70.**
- **Time taken to report fallen from 3 months to 4-6 weeks**

Mutation found in 40% of patients with a clinical diagnosis of FH
Overall ~ 50-60% of clinical FH patients have no mutation found

Polygenic Cause of no mutation FH

HYPOTHESIS: Having a large number of common genetic variants that each raise LDL-C by a small amount could mimic Monogenic FH


Use of low-density lipoprotein cholesterol gene score to distinguish patients with polygenic and monogenic familial hypercholesterolaemia: a case-control study

Philippa J Talmud*, Sonia Shah*, Ros Whittall, Marta Futema, Philip Howard, Jackie A Cooper, Seamus C Harrison, KaWah Li, Fotios Drenos, Frederik Karpe, H Andrew W Neil, Olivier S Descamps, Claudia Langenberg, Nicholas Lench, Mika Kivimaki, John Whittaker, Aroon D Hingorani, Meena Kumari, Steve E Humphries

Talmud et al Lancet 2013

- **GWAS had identified > 90 SNPs → modest LDL-C raising**
- **Used 12 common LDL-Raising SNPs to construct a "weighted" Polygenic Risk Score (PRS)**
- **Compared mean PRS in 321 UK mutation -ve FH patients and 451 from Belgium vs 3000 healthy subjects (Whitehall II study)**
- **Results in UK non-mutation FH patients show that in at least 80% a "polygenic" cause of their elevated LDL-C is most likely explanation**
- **Results confirmed in Belgium patients and in samples from 7 other countries - Futema et al Clin Chem 2015, Mariano et al Clin Genet 2020.**

Weighted Gene Score in FH/M- vs WHII

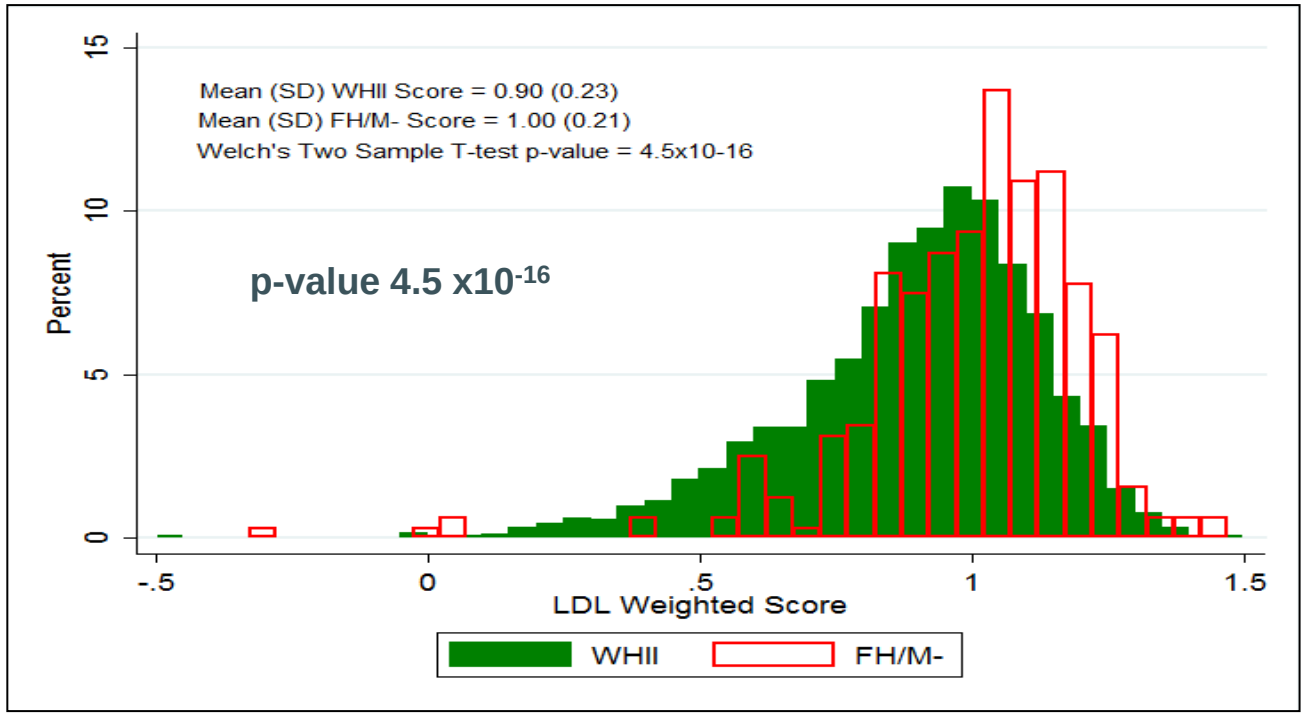
Talmud et al Lancet 2013

Developed PRS based on SNPs identified by Global Lipid Genetics Consortium (GLGC) (Teslovitch et al, Nature, 2010)

CHR	SNP	Gene	A1	A2	Beta
1	rs2479409	***PCSK9***	G	A	0.052
1	rs629301	*CELSR2*	G	T	0.15
2	rs1367117	***APOB***	A	G	0.10
2	rs6544713	*ABCG8*	T	C	0.07
6	rs3757354	*MYLIP*	T	C	0.037
6	rs1800562	*HFE*	A	G	0.057
6	rs1564348	*SLC22A1*	C	T	0.014
11	rs11220462	*ST3GAL4*	A	G	0.05
14	rs8017377	*KIAA1305*	A	G	0.029
19	rs6511720	***LDLR***	T	G	0.18
19	rs7412	*APOE*	ε3	ε2	-0.4
19	plus	*APOE*	ε3	ε3	0.0
19	rs429358	*APOE*	ε3	ε4	0.1

Improved precision by scaling for size of effect of each SNP - Weighted Score

FH/M- Mean weighted score

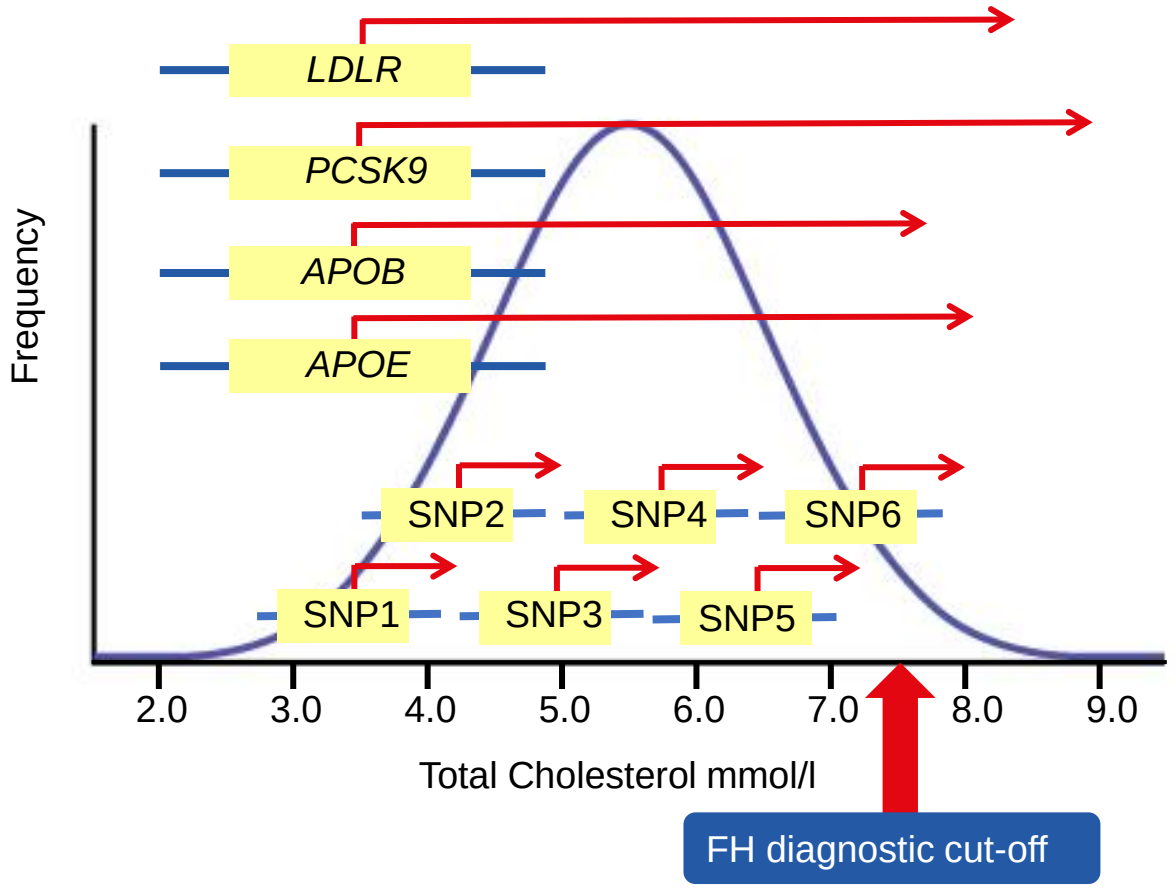


54% of FH/M- are in the top three deciles of score vs 11% in the lowest three deciles

Monogenic & Polygenic causes of high Cholesterol

You can be above diagnostic threshold because of :

1. having a pathogenic mutation in a single gene or by
2. the combination of > average number of common variants



CHD in Monogenic versus Polygenic FH

Greater preclinical atherosclerosis in treated monogenic familial hypercholesterolemia *vs.* polygenic hypercholesterolemia

Mahtab Sharifi [a, b], Elizabeth Higginson [c], Sven Bos [d], Angela Gallivan [b], Darren Harvey [b], Ka Wah Li [a], Amali Abeysekera [c], Angela Haddon [c], Helen Ashby [c], Kate E. Shipman [c], Jackie A. Cooper [a], Marta Futema [e], Jeanine E. Roeters van Lennep [d], Eric J.G. Sijbrands [d], Mourad Labib [c], Devaki Nair [b], Steve E. Humphries [a, *]

Atherosclerosis 2018

Aims:

To compare the extent of atherosclerosis in individuals with a clinical diagnosis of FH and similar LDL-C levels but with a monogenic vs polygenic aetiology

Methods

Recruited from outpatient lipid clinics in UK, (Royal Free Hospital, London and Russells Hall Hospital, Dudley), Netherlands, Erasmus Medical Centre, Rotterdam,

Carotid IMT was measured in B-mode by a Philips CX50 machine equipped with a 5-10 MHz linear array probe.

CAC was measured using Symbia TruePoint T6 SPECT/CT scanner (Siemens) in UK and dual-source CT scanner Somatom Definition FLASH, Siemens in Holland.

Patient Demographics Royal Free

	Monogenic N=56	Polygenic N=30	P value
Male	40	47	
Age	50 (14)	57 (12)	0.03
TC mmol/l	8.1 (1.5)	8.2 (1.0)	0.5
LDL-C mmol/l	5.8 (1.6)	5.9 (0.9)	0.8
HDL-C mmol/l	1.5 (0.4)	1.9 (1.1)	0.1
TG mmol/l	1.2 (0.5)	1.6 (0.7)	0.01
%age on LLT	75	85	0.7

Polygenic older and higher TG but well-matched for LDL-C

CIMT Results

cIMT after Adjus't for Age and Gender

	Monogenic	Polygenic	P value
	Mean (95%CI)	Mean (95%CI)	
Mean-cIMT	0.74 (0.70 - 0.79)	0.66 (0.61 - 0.72)	0.03
Mean CCA	0.65 (0.61 - 0.68)	0.62 (0.58 - 0.66)	0.3
Max CCA	0.72 (0.68 - 0.77)	0.70 (0.64 - 0.76)	0.5
Mean bulb	0.81 (0.74 - 0.89)	0.70 (0.62 - 0.79)	**0.05**
Max bulb	0.96 (0.85 - 1.07)	0.80 (0.69 - 0.93)	0.08
Mean ICA	0.74 (0.66 - 0.83)	0.60 (0.52 - 0.70)	**0.04**
Max ICA	0.82 (0.69 - 0.96)	0.65 (0.52 - 0.81)	0.1

Monogenic have ~12% thicker cIMT

CT Coronary Angiogram (CTCA)

- Coronary artery disease severity score
- Assessment of plaque burden/morphology
- The total plaque volume
- Calcified and non-calcified volume
- Recruited patients from Holland and UK

CAC score	Monogenic N = 124	Polygenic N = 42	p value
	mean (95% CI)	mean (95% CI)	
UK	33.45 (13.9-81.5)	1.05 (0.32 -3.44)	
Netherlands	22.9 (12.1-43.4)	11.1 (2.3 – 54.0)	
Total	24.5 (14.4-41.8)	2.65 (0.94 -7.44)	0.0004

CAC score 9.27 x higher in the monogenic compared to the polygenic group after adjustment for centre, age and gender (p=0.0004).

> CAD risk in Monogenic vs Polygenic high LDL-C

JAMA Cardiology | Original Investigation

Association of Monogenic vs Polygenic Hypercholesterolemia With Risk of Atherosclerotic Cardiovascular Disease

Mark Trinder, MSc; Gordon A. Francis, MD; Liam R. Brunham, MD, PhD

JAMA Cardiol. 2020;5(4):390-399.

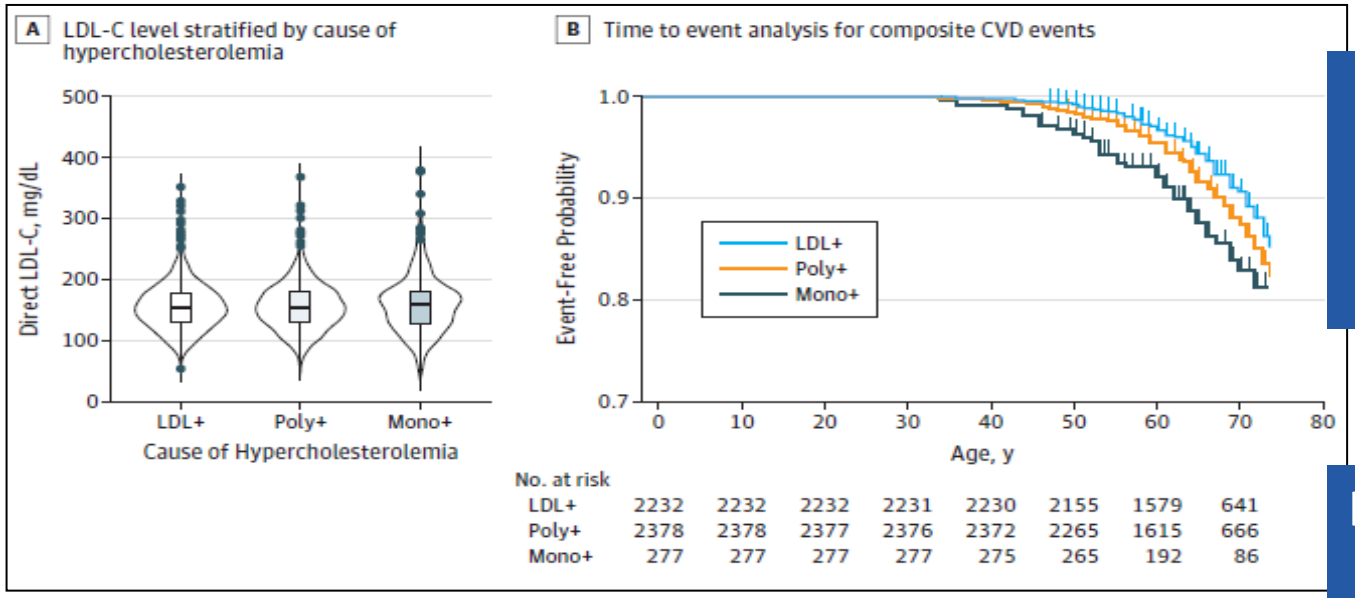
Aims:

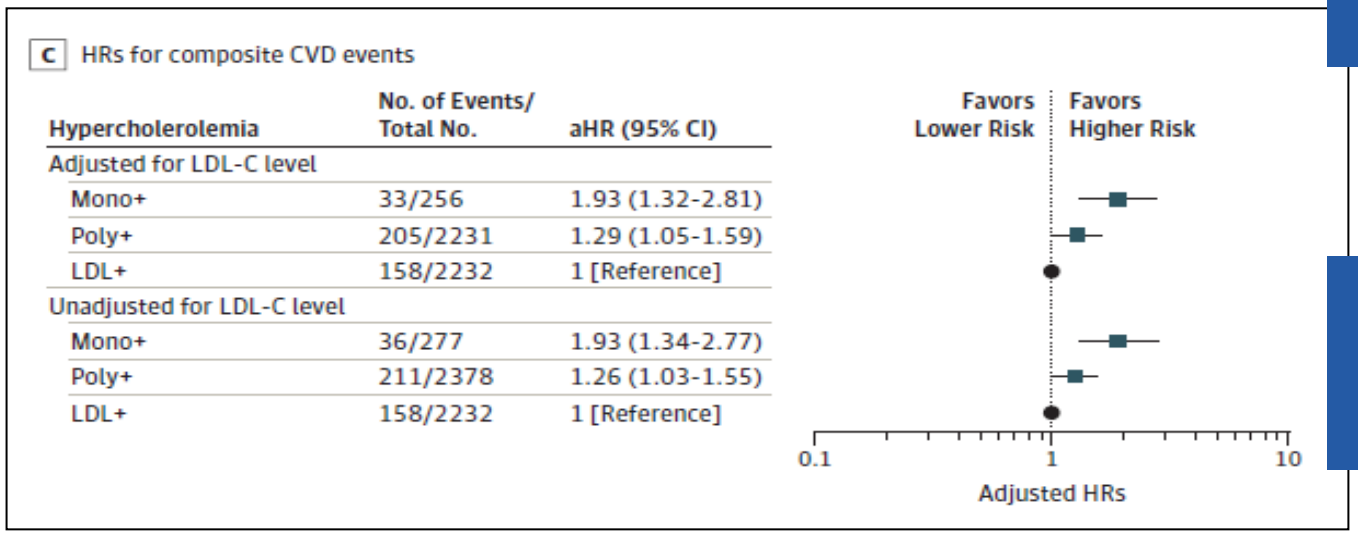
To compare CVD risk in those with monogenic FH (mFH), polygenic hypercholesterolaemia (PGH),vs nongenetic hypercholesterolemia (NGH)

DESIGN, SETTING, AND PARTICIPANTS:

- UK Biobank, (40-69 yrs). Genotyping array and exome sequencing →
- Those with monogenic FH (*LDLR*, *APOB*, and *PCSK9 n = 277*)
- PGH (LDL-C polygenic score >95th percentile based on 223 SNPs in the entire cohort (n = 2379), vs NGH (n = 2379).
- CVD = Revascularisation, MI, Stroke, plus all-cause mortality.

Hazard Ratio for CVD risk in mFH vs PGH vs NGH





Overall HR in mFH vs rest of sample = 1.78 (1.3-2.5; *P* < .001).
For those < 55 years HR = 3.17 (1.96-5.12; *P* < .001).

Highest "LDL-C Burden" in mFH, lower in PGH, and lowest in NGH. Conclusion : PRS has clinical utility

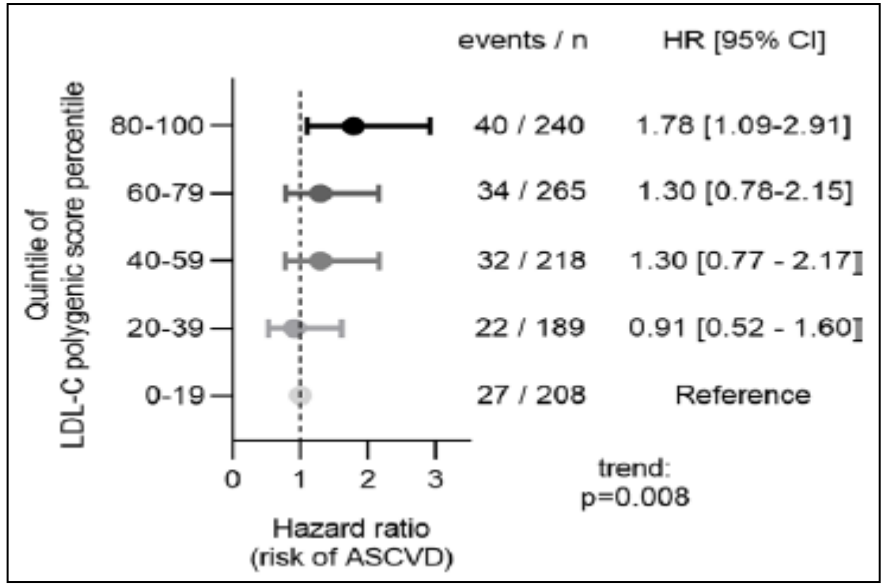
Compared to non genetic high LDL-C, Polygenic High LDL-C → ~30% higher CVD risk and mFH → ~2 fold higher

What about use of LDL PRS in FH patients?

- Mounting evidence that individuals with clinical FH and both a monogenic cause and a high PRS have > CVD risk than those with monogenic FH and a low score (Trinder et al 2019, Trinder et al 2020)
- In a meta-analysis of ~1000 M+ve FH, those with PRS >80th %ile had a 78% higher HR for CVD vs <20th
- This risk was in part but not fully explained by their higher LDL-C.

PMID: 33079599

HR for ASCVD



Based on this data it is appropriate to consider using intense lipid-lowering therapy and even lower LDL-C on-treatment targets for those with a PRS > 8th decile

How Many M+ FH are currently Known?

Kate Haralambos

- Since 2014 BHF have “seed-corn” funded 29 FH Nurses in 12 centres
- Covers ~50% of the UK population
- PASS database (HEARTUK) allows regular updates

	NI	Wales	Scotland	England*	Total UK
Population covered (million)	1.87	3.17	5.37	22.9	39.61
Year began Genetic Testing	2000	2005	2008	2003-5	
% Identified (using 1 in 270)	21.4%	12.2%	10.6%	5.8%	7.7%
Index Positive	343	643	1081	3059	5126
Index Negative	2767	2189	5782	7991	18729
Index VUS	30	92	160	401	683
Diagnostic yield	10.9%	21.9%	15.4%	26.7%	20.9%
Positive Relatives	1136	792	1028	3232	6188
Negative Relatives	1237	661	1073	3174	6145
Rels tested per POS index	6.9	2.3	1.9	2.1	2.4
POS Rels per POS index	3.3	1.2	1.0	1.1	1.2
Total Positives (not inc VUS)	1479	1435	2109	6291	11314

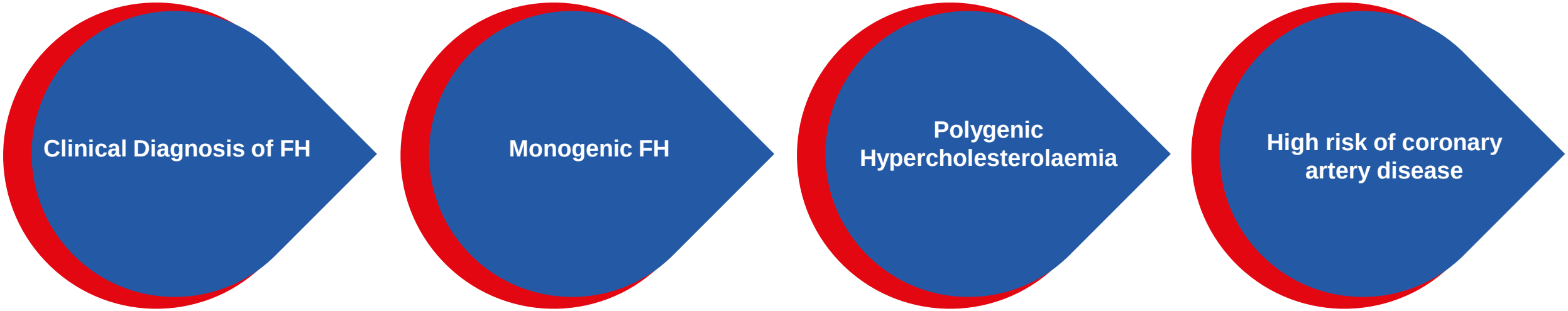
- **To date ~24,500 index and >12,000 relative genetic tests**
- **→ 5126 M+ve index cases**
- **and 6188 M+ve relatives**
- **of whom >460 are under 20yrs**

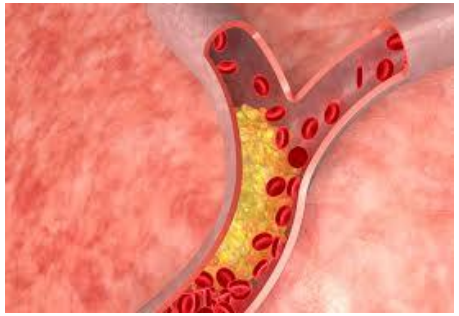
~8% of predicted FH in UK!

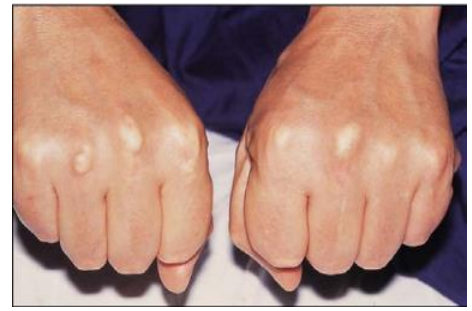
Need to fund ~150 nurses over UK to → >25% of FH patients within 5 years

* Some centres only started 2017-18

Summary


Clinical Diagnosis of FH
Monogenic FH
Polygenic Hypercholesterolaemia
High risk of coronary artery disease





03

Management of Familial Hypercholesterolaemia

Dr Jaimini Cegla

MRCP FRCPath PhD Consultant in Chemical Pathology and Metabolic Medicine Hammersmith Hospital Lipid Clinic

An unrecognised, potentially fatal, treatable disease

Genetic disorder – we know the genes involved

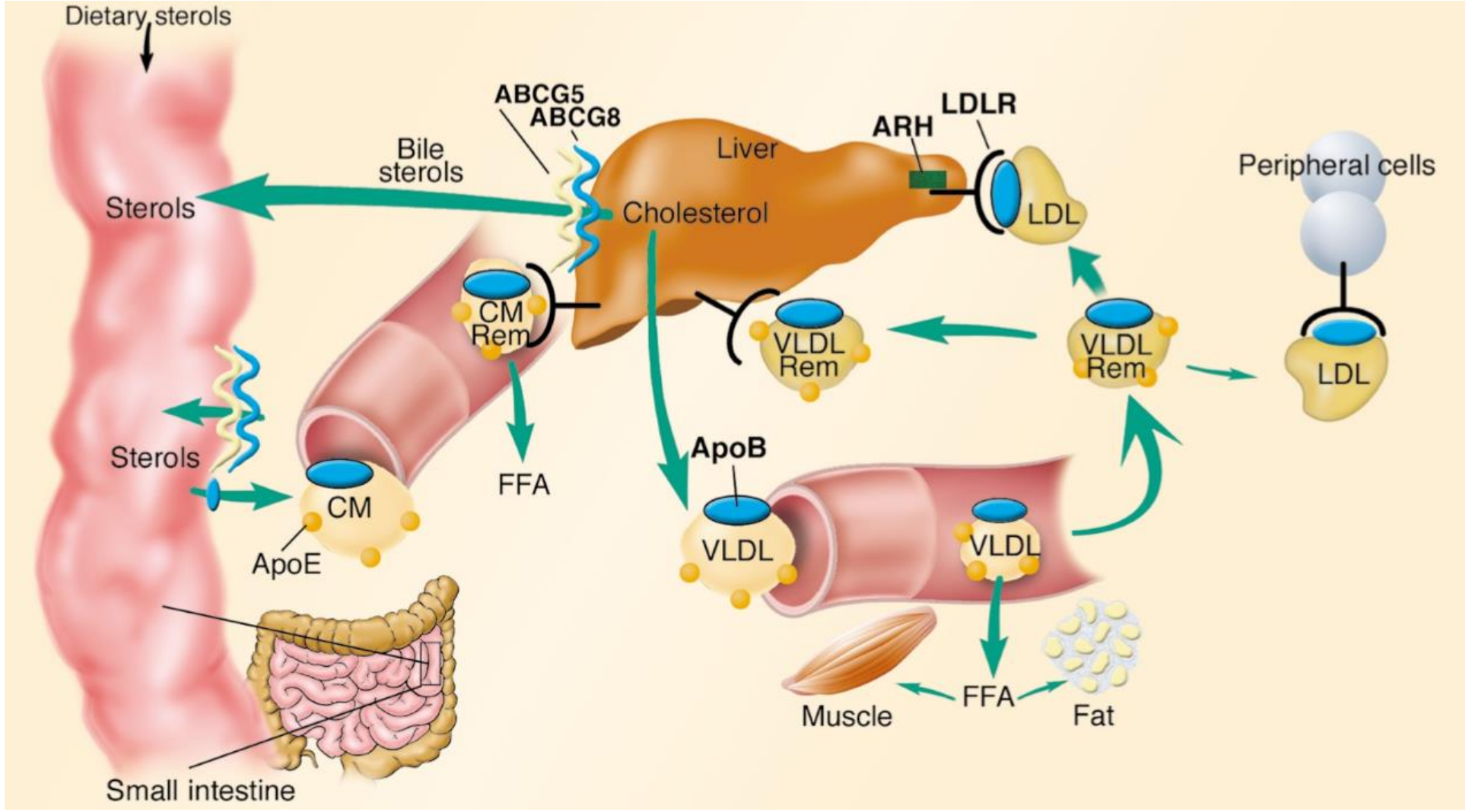
Common –as Type 1 DM

50% men will have MI by age of 50 and 60% of women by age of 60

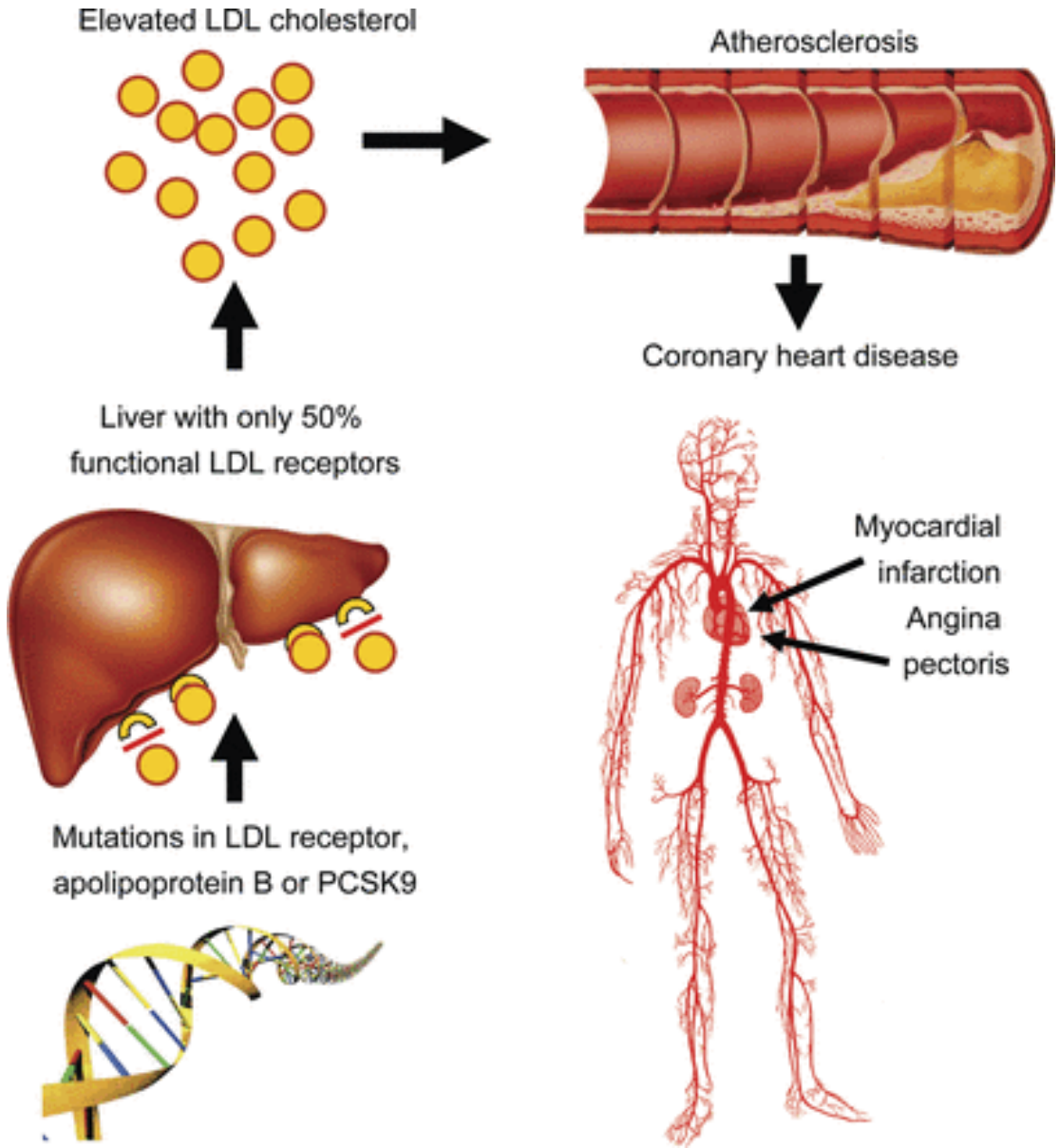
Treatable

Underdiagnosed

LDL metabolism

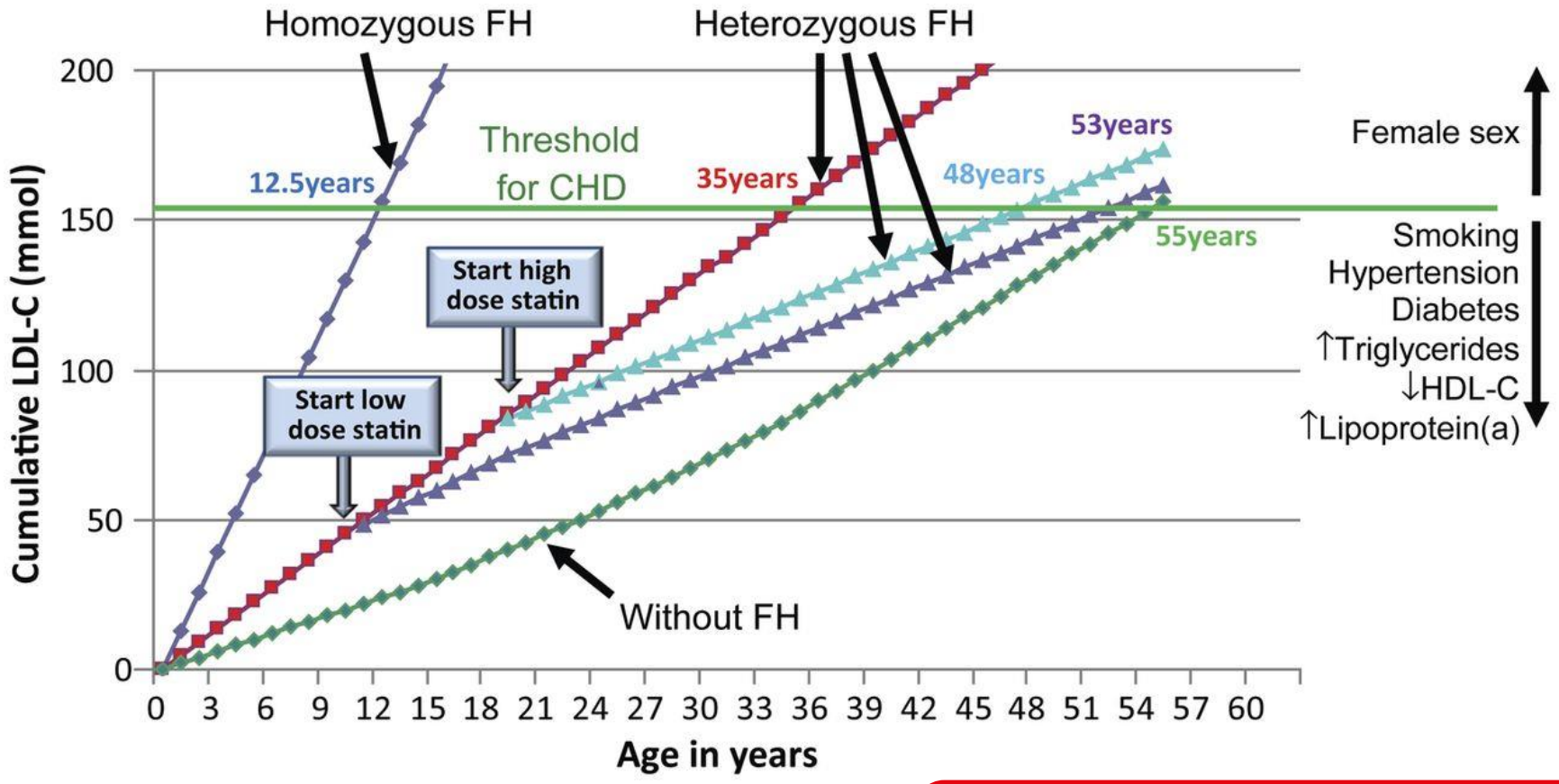


Hobbs et al; J Clin Inv, 2003



Nordestgaard et al; Eur Heart J, 2013

Why do FH patients have such premature CHD?



LDL-Burden = LDL-C level x years exposure

Nordestgaard et al; Eur Heart J, 2013

Management

Lifestyle modification

LDL lowering drugs

- Statins
- Ezetemibe
- Bile acid sequestrants
- PCSK9 mab
- Bempedoic acid
- Inclisiran

LDL-Apheresis

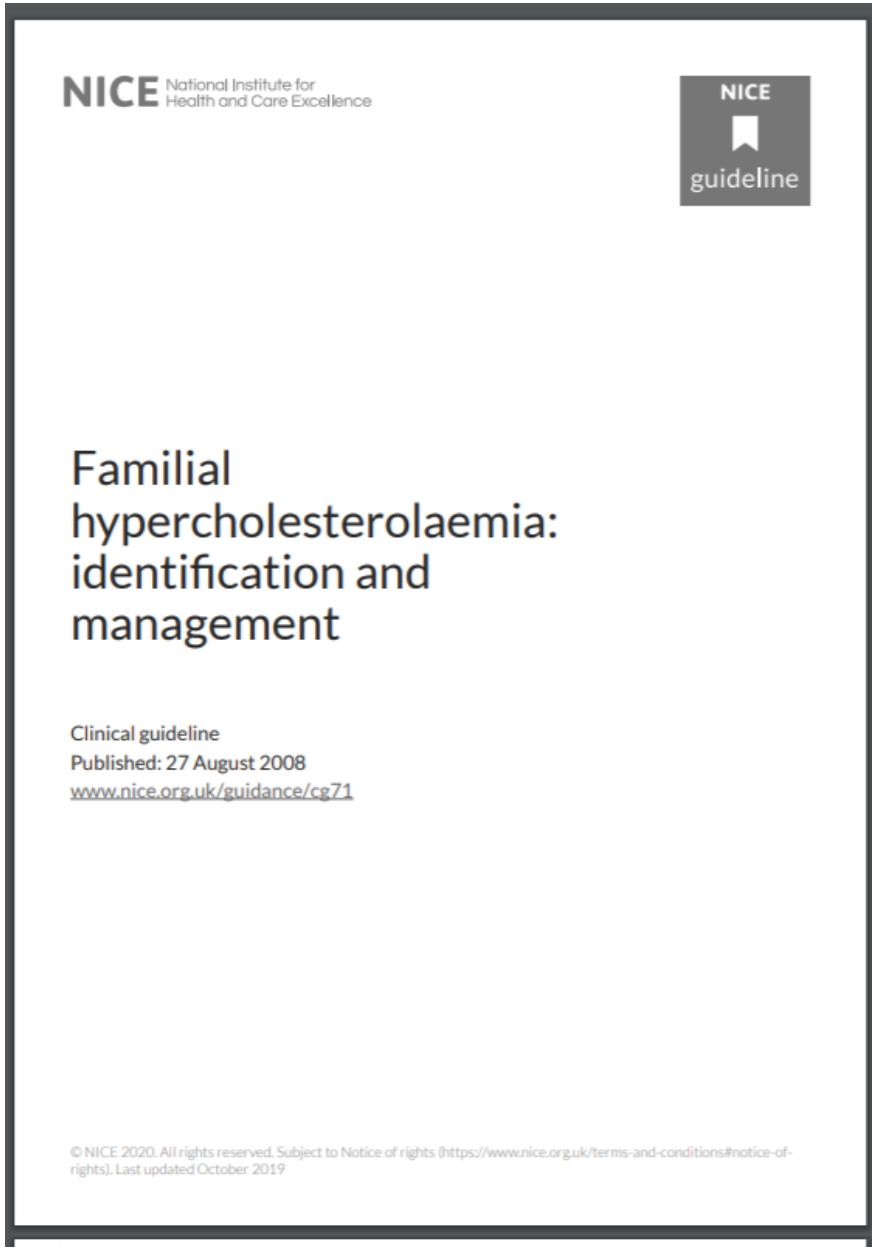
Assess additional CVD risk factors

Presence of additional CVD risk factors should guide the intensity of management

- Hypertension, diabetes, obesity, smoking
- Lipoprotein(a)
- Level and duration of untreated LDL cholesterol
- Prematurity of the family & personal history of CVD
- **Q-RISK and other CVD risk equations should not be used**

Cardiovascular imaging may be useful for assessing asymptomatic patients

- Cardiac computed tomography+/-angiography
- Carotid ultrasonography
- Clinical value of imaging not fully established



NICE National Institute for Health and Care Excellence

NICE guideline

Familial hypercholesterolaemia: identification and management

Clinical guideline
Published: 27 August 2008
www.nice.org.uk/guidance/cg71

Lifestyle

- Regard lifestyle advice as a component of medical management, and not as a substitute for lipid-modifying drug therapy. **[2008]**

- Diet
- Physical activity
- Weight management
- Alcohol consumption
- Smoking advice

NICE CG71

Adults

- Lipid-modifying drug therapy should be lifelong. **[2008]**.
- Offer high-intensity statin as initial treatment and aim for ≥ 50% reduction in LDL-C from baseline. **[2017]**
- Ezetimibe monotherapy if statin therapy is contraindicated or not tolerated or co-administered with statin when LDL-C not appropriately controlled[1] **[2016]**

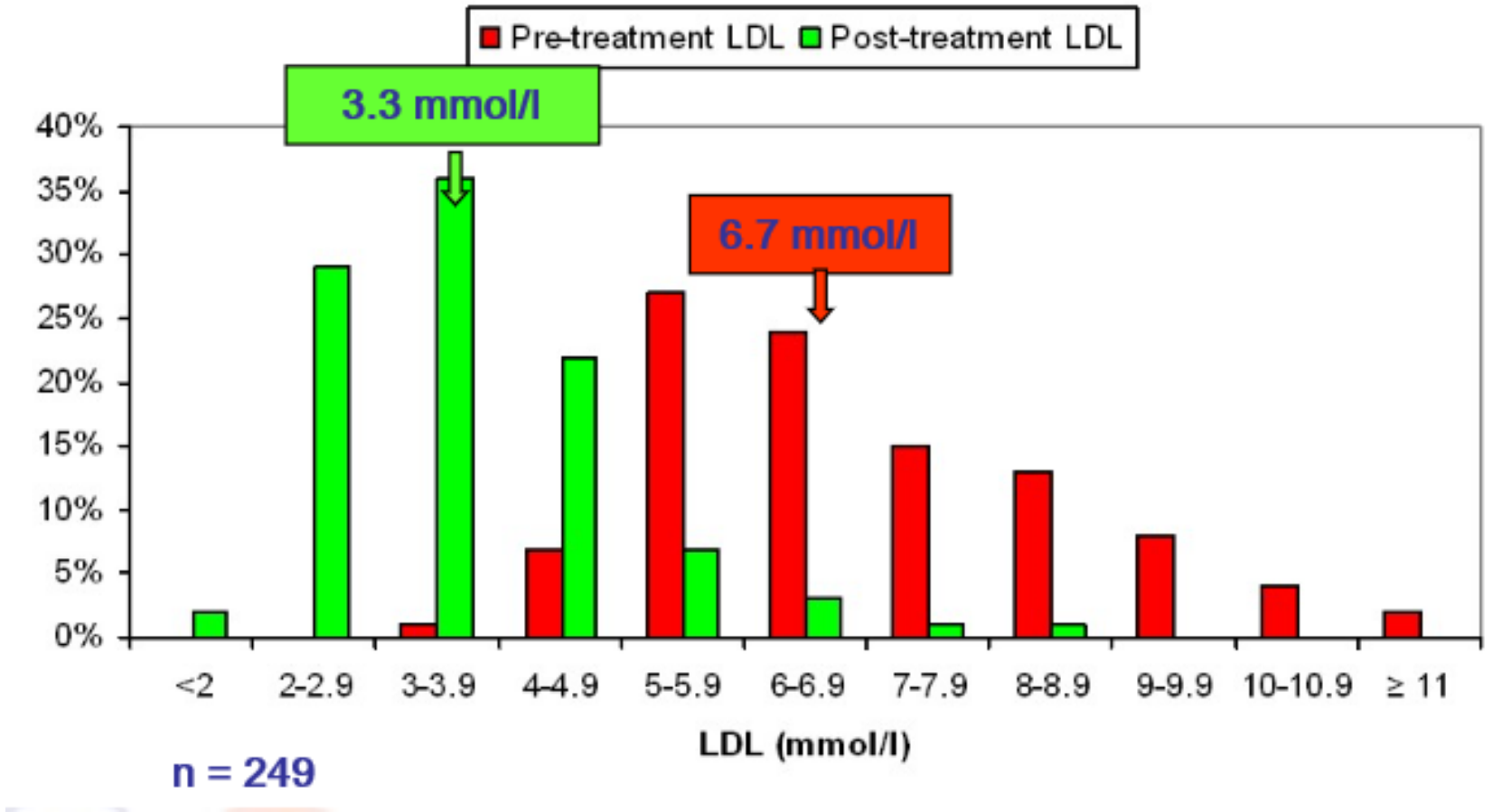
Refer to specialist FH service for the following:

- Maximum tolerated dose of a high-intensity statin and ezetimibe does not achieve a recommended reduction in LDL-C of greater than 50% from baseline. **[2008]**
- At very high risk of a coronary event:
    - Established coronary heart disease.
    - A family history of premature CHD.
    - Two or more other CV risk factors (eg male, smoke, hypertension or diabetes). **[2008]**
- Consider bile acid seq/fibrate if intolerance/contraindications to statins/ezetimibe, **[2008, amended 2017]**
- If LDL-C not controlled despite maximal tolerated see the NICE tech appraisal on PCSK9 inhibition. **[2017]**

1. Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia. NICE Technology appraisal guidance [TA385]: 24 February 2016

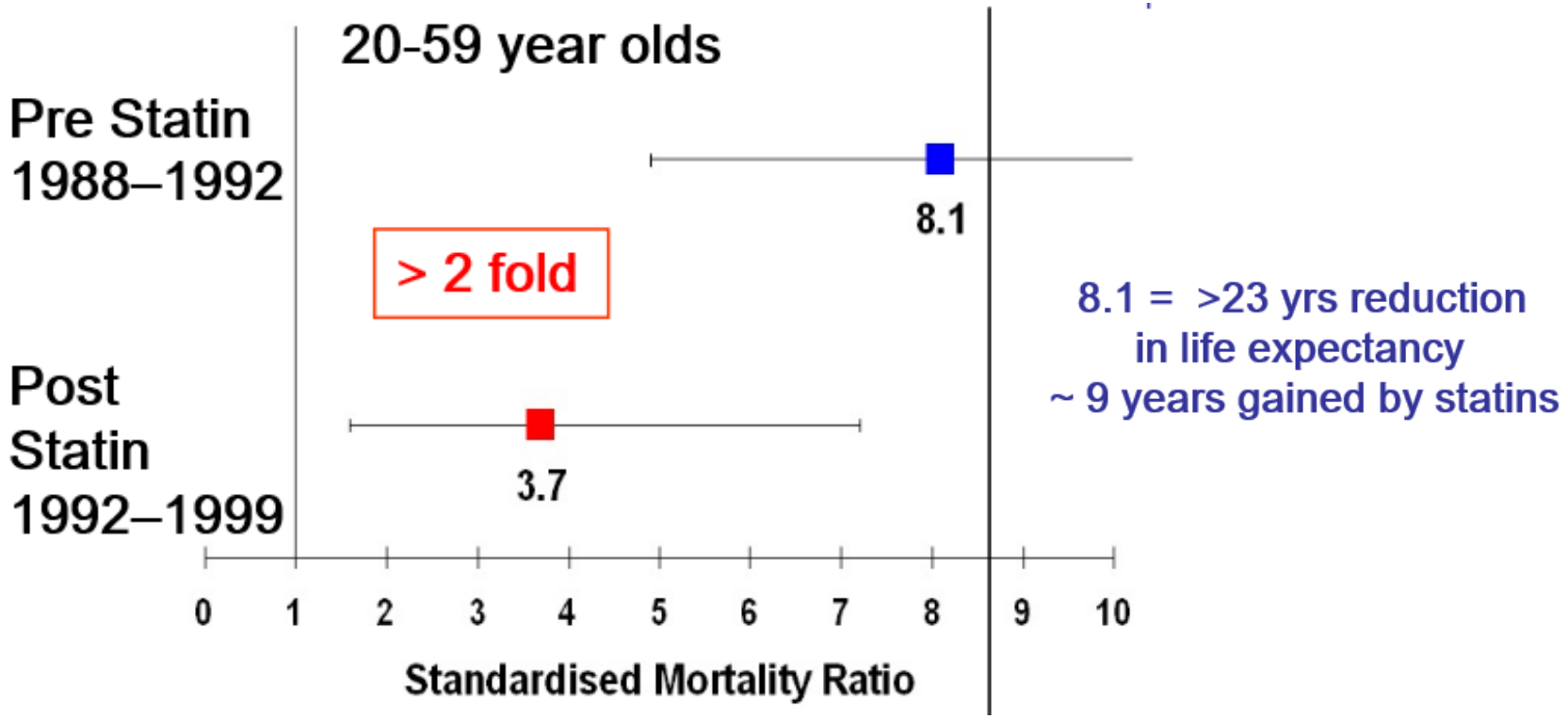
NICE CG71

Can LDL be lowered in FH patients?



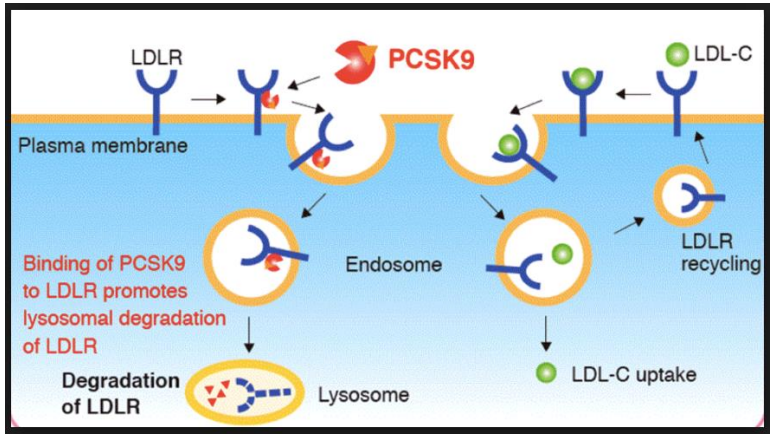
Hadfield et al; 2007

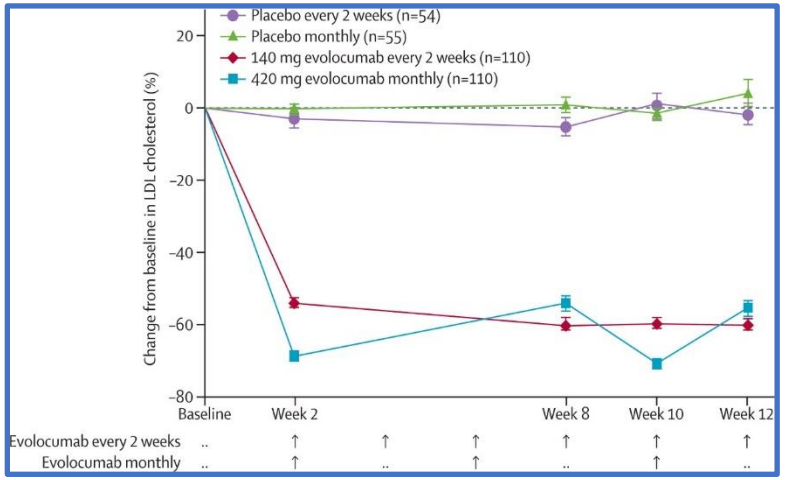
Statins decrease mortality in FH



Simon Broome UK FH Registry papers; Athero, 1999

PCSK9 mAbs





Raal et al, Lancet. 2015

	Without CVD	With CVD	
		High risk of CVD [1]	Very high risk of CVD [2]
Primary non-familial hypercholesterolaemia or mixed dyslipidaemia	Not recommended at any LDL-C concentration	Recommended only if LDL-C concentration is persistently above 4.0 mmol/litre	Recommended only if LDL-C concentration is persistently above 3.5 mmol/litre
Primary heterozygous-familial hypercholesterolaemia	Recommended only if LDL-C concentration is persistently above 5.0 mmol/litre	Recommended only if LDL-C concentration is persistently above 3.5 mmol/litre	

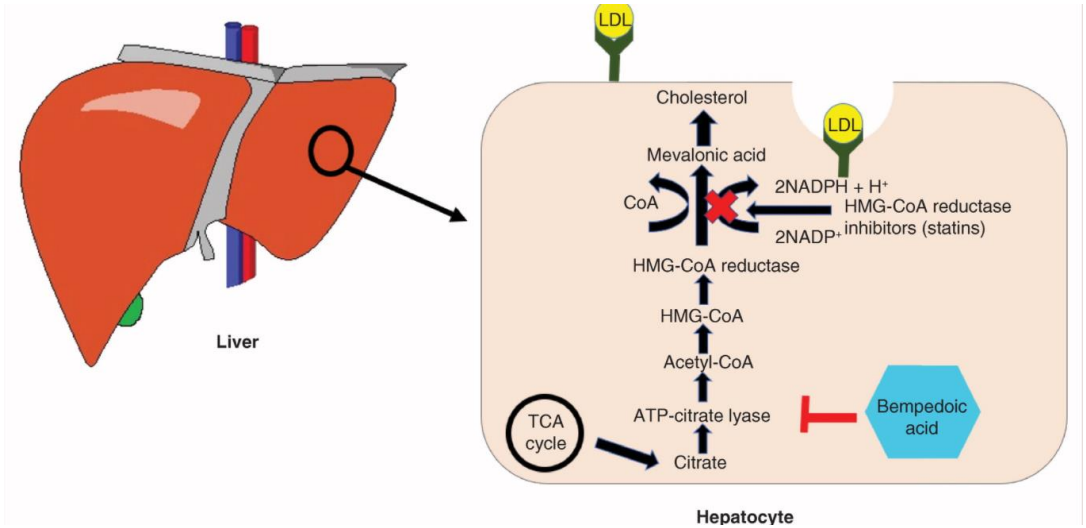
[1] High risk of CVD is defined as a history of any of the following: acute coronary syndrome (such as myocardial infarction or unstable angina needing hospitalisation); coronary or other arterial revascularisation procedures; coronary heart disease; ischaemic stroke; peripheral arterial disease.

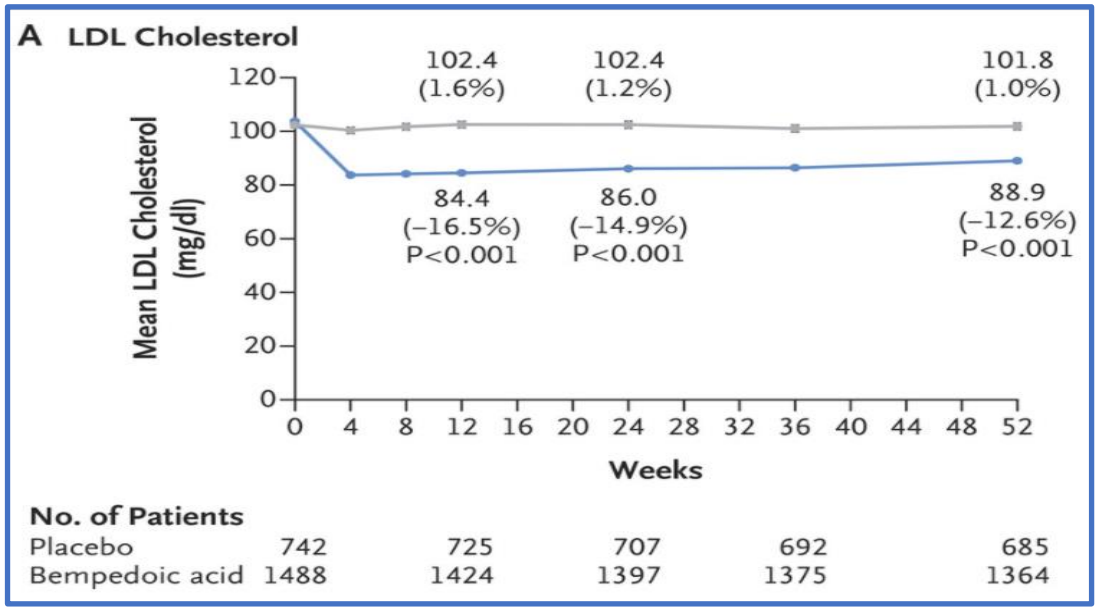
[2] Very high risk of CVD is defined as recurrent cardiovascular events or cardiovascular events in more than 1 vascular bed (that is, polyvascular disease).

Abbreviations: CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

NICE TA394

Bempedoic Acid





Ray et al, NEJM. 2019

Bempedoic Acid and NICE

1 Recommendations

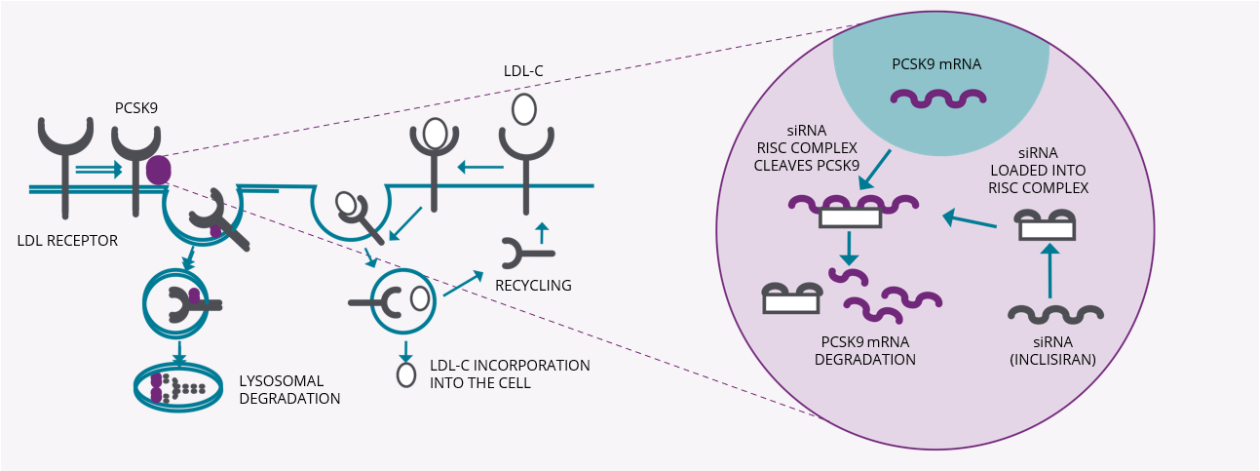
1.1 Bempedoic acid with ezetimibe is recommended as an option for treating primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia as an adjunct to diet in adults. It is recommended only if:

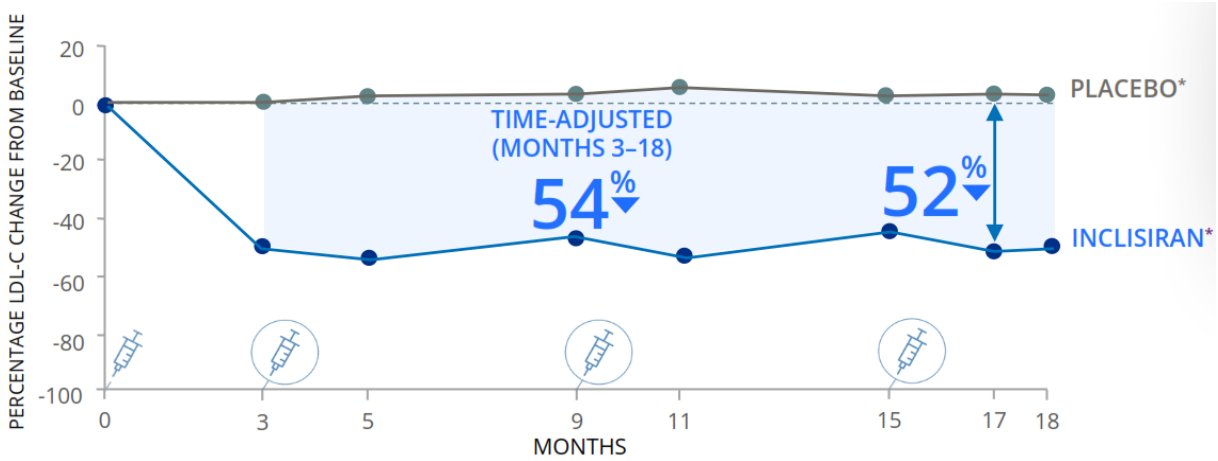
- statins are contraindicated or not tolerated
- ezetimibe alone does not control low-density lipoprotein cholesterol well enough and
- the company provides bempedoic acid and bempedoic acid with ezetimibe according to the commercial arrangement.

Bempedoic acid with ezetimibe can be used as separate tablets or a fixed-dose combination.

NICE TA694

Inclisiran





No. of Patients								
Placebo	780	762	745	724	715	698	666	670
Inclisiran	781	758	757	737	731	721	691	705

* Reductions were achieved on top of a maximally tolerated statin and/or other lipid-lowering therapies. Adapte from Ray KK et al. N Engl J Med 2020[1]

Inclisiran and NICE

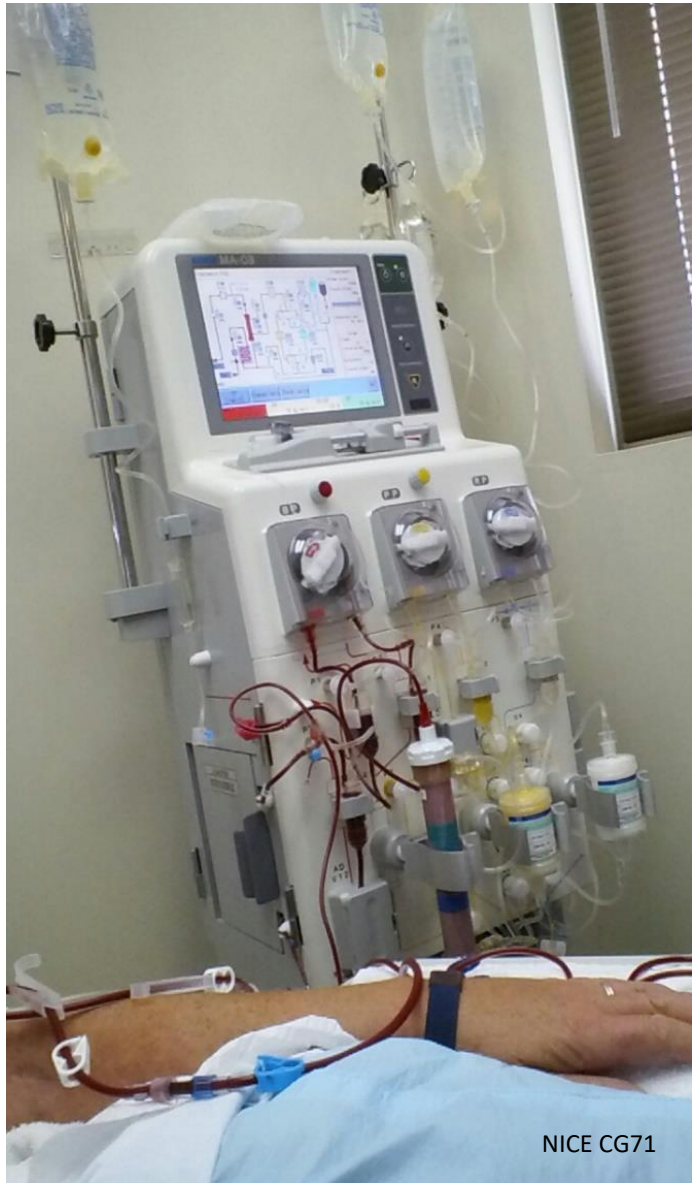
Inclisiran is recommended as an option for treating primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia as an adjunct to diet in adults. It is recommended only if:

- there is a history of any of the following cardiovascular events:
  - acute coronary syndrome (such as myocardial infarction or unstable angina needing hospitalisation)
  - coronary or other arterial revascularisation procedures
  - coronary heart disease
  - ischaemic stroke or
  - peripheral arterial disease, and
- low-density lipoprotein cholesterol (LDL-C) concentrations are persistently 2.6 mmol/l or more, despite maximum tolerated lipid-lowering therapy, that is:
  - maximum tolerated statins with or without other lipid-lowering therapies or,
  - other lipid-lowering therapies when statins are not tolerated or are contraindicated, and

NICE TA733

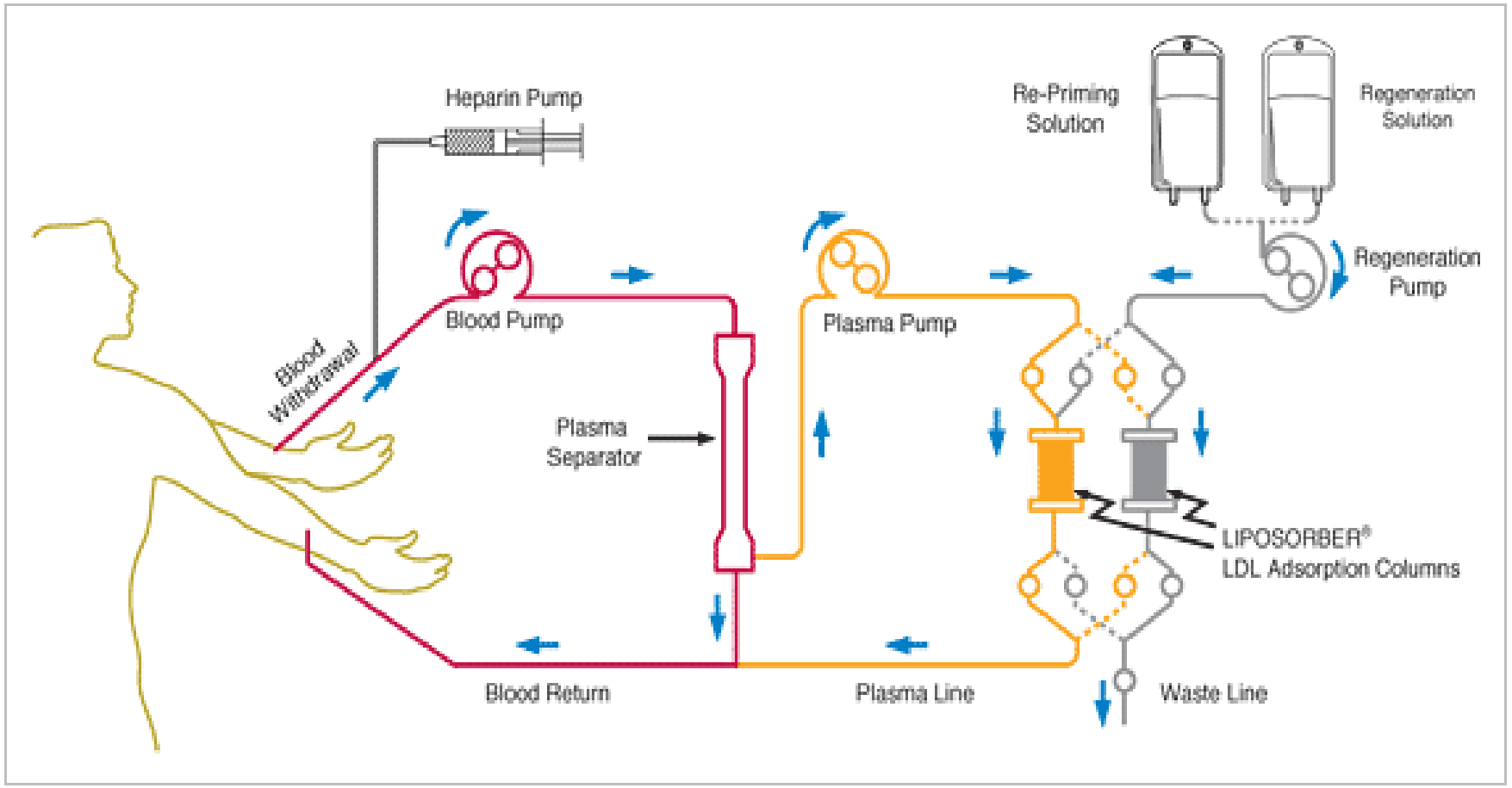
LDL-lowering apheresis

- Consider LDL apheresis in homozygous FH. The timing will depend on response to drug therapy and presence of coronary heart disease. **[2008]**
- In exceptional instances, consider LDL apheresis for heterozygous FH. This should take place in a specialist centre on a case-by-case basis and data recorded in an appropriate registry. **[2008]**
- Recommend arterio-venous fistulae as the preferred method of access. **[2008]**



NICE CG71

Lipoprotein apheresis how it works



Comparison of guideline targets

Primary or secondary target	Treatment target	Unit	AACE[131]	ESC/EAS[38]	CCS[69]	AHA/ACC[44]	NLA[132]	JAS[42]	NICE[133,134]
Primary prevention									
Primary	Relative LDL-cholesterol level reduction	% from baseline	–	≥50	50	–	≥50	≥50	>50[a]
	Absolute LDL-cholesterol level	mmol/l	<1.8	<1.8[b]	<2.5[c]	<2.6[d]	<2.6	<2.6	–
		mg/dl	<70	<70	<97	<100	<100	<100	–
Secondary	Absolute non-HDL-cholesterol level	mmol/l	<2.6	<2.6	–	–	<3.4	–	–
		mg/dl	<100	<100	–	–	<130	–	–
	Absolute apoB level	mg/dl	<80	<80	–	–	<90	–	–
Secondary prevention									
Primary	Relative LDL-cholesterol level reduction	% from baseline	–	≥50	–	–	≥50	–	>50[c]
	Absolute LDL-cholesterol level	mmol/l	<1.4	<1.4	<2.0	<1.8	<1.8	<1.8	–
		mg/dl	<55	<55	<77	<70	<70	<70	–
Secondary	Absolute non-HDL-cholesterol level	mmol/l	<2.1	<2.2	<2.6	<2.6	<2.6	–	–
		mg/dl	<80	<85	<100	<100	<100	–	–
	Absolute apoB level	mg/dl	<70	<65	–	–	<80	–	–

[a]Use a threshold of >5.0 mmol/l to consider using a PCSK9 inhibitor as third-line therapy.
[b]Lower target to <1.4 mmol/l if another major risk factor (eg. smoking, DM, hypertension or unequivocal ASCVD on imaging).
[c]Use a threshold of >3.5 mmol/l to consider using a PCSK9 inhibitor as third-line therapy.

Adapted from Watts et al, Nature Rev Cardiol 2020

Children and young people

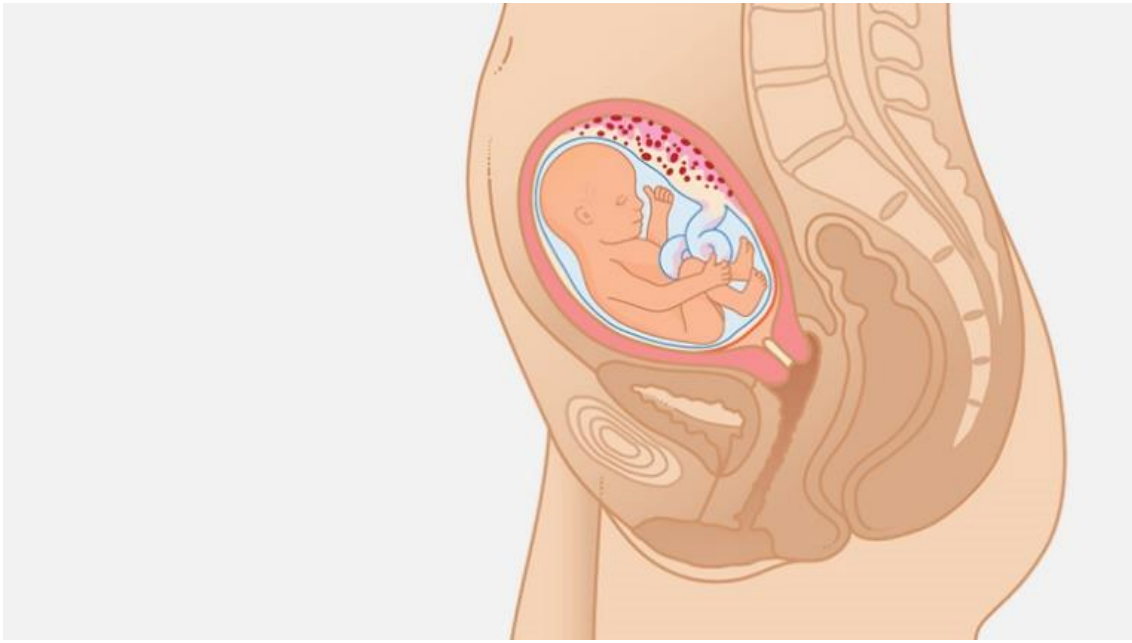
- Seen by specialist FH service in an appropriate child/young person-focused setting **[2008]**
- Lipid-modifying therapy considered by the age of 10 years depending on:
  - their age
  - the age of onset of CHD within the family, and
  - the presence of other CV risk factors, including their LDL-C . **[2008]**
- In exceptional instances, consider offering:
  - a higher dose of statin than is licensed for use in the appropriate age group, **and/or**
  - more than one drug therapy, **and/or**
  - drug therapy before the age of 10 years. **[2008]**
- If intolerant of statins, consider bile acid sequestrants, fibrates or ezetimibe. **[2008]**
- Routine monitoring of growth and pubertal development. **[2008]**
- In homozygous FH, LDL-C may be lowered by lipid-modifying drug therapy and this should be considered before LDL apheresis. **[2008]**

NICE CG71

Contraception and pregnancy

- **Contraception for women and girls with FH**
- Discuss the risks for future pregnancy and the foetus while taking lipid-modifying drug therapy at least annually. **[2008]**
- Combined oral contraceptives (COCs) are not generally contraindicated with lipid-modifying drug therapy. **[2008]**

- **Information for pregnant women with FH**
- No reason to advise against pregnancy or breastfeeding in women with FH. **[2008]**
- Lipid-modifying drug therapy should be stopped 3 months before conception and pregnancy **[2008]**
- Women with FH who conceive while taking statins or other systemically absorbed lipid-modifying drug therapy should be advised to stop treatment immediately and they should be offered an urgent referral to an obstetrician for a fetal assessment. **[2008]**
- Shared-care arrangements, to include expertise in cardiology and obstetrics, essential for women with homozygous FH. **[2008]**
- Serum cholesterol should not be measured routinely during pregnancy. **[2008]**
- Resins are the only lipid-modifying drug therapy that should be considered during lactation. **[2008]**



NICE CG71

Summary: An unrecognised, potentially fatal, treatable disease

Genetic disorder – we know the genes involved

Common –as Type 1 DM

50% men will have MI by age of 50 and 60% of women by age of 60

Treatable

Underdiagnosed

04

Identification of FH cases in primary care

Professor Nadeem Qureshi
Professor of Primary Care, University of Nottingham,
PRISM research group

The following slide deck is courtesy of the University of Nottingham PRISM research group

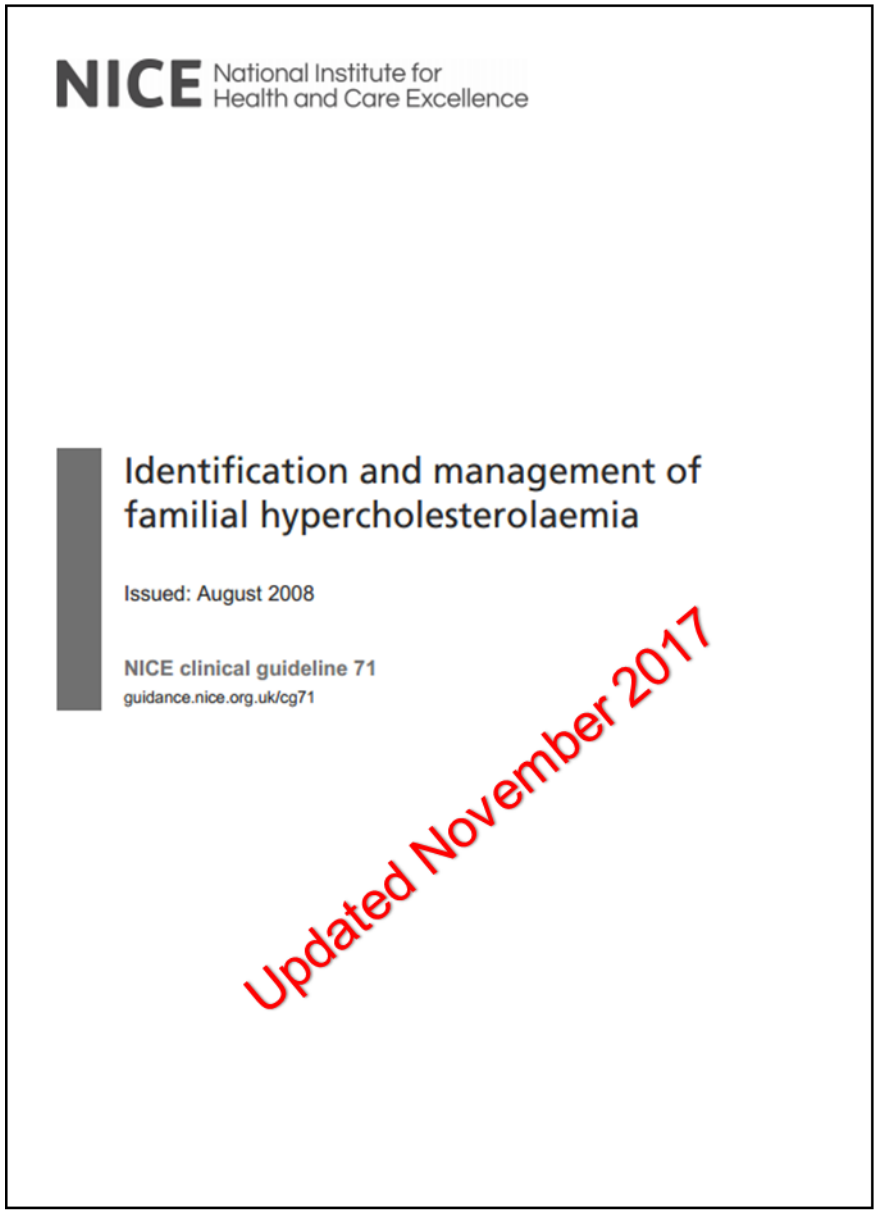
University of Nottingham
UK | CHINA | MALAYSIA

Translation to Practice:

Improving identification of familial hypercholesterolaemia in primary care

Professor Nadeem Qureshi
PRISM research group

Familial Hypercholesterolaemia



Simon Broome Criteria	
a	Total cholesterol concentration >7.5 mmol/L or LDL-C > 4.9 mmol/L in adults Total cholesterol concentration >6.7 mmol/L or LDL-C > 4.0 mmol/L in children aged <16 years
b	Tendon xanthoma in the patient or a first or second degree relative
c	DNA-based evidence of mutation in the LDLR, APOB or PCSK9 mutation
d	Family history of myocardial infarction before age 50 years in a second degree relative or before age 60 years in a first degree relative
e	Family history of raised total cholesterol > 7.5 mmol/L in an adult first or second degree relative Family history of raised total cholesterol > 6.7 mmol/L in a child, brother or sister aged 16 years or younger
Diagnosis	
Definite Familial Hypercholesterolaemia: criteria a and b, or criteria c Probable Familial Hypercholesterolaemia: criteria a and d, or criteria a and e	

Dutch Lipid Clinic Criteria	Point
Family history	
First degree relative with known premature coronary and vascular disease OR First degree relative with known LDL-C level above the 95th percentile	1
First degree relative with tendinous xanthomata and/or arcus cornealis OR Children aged less than 18 years with LDL-C above the 95th percentile	2
Clinical history	
Patient with premature (men <55 years; women <60 years) coronary artery disease	2
Patient with premature (men <55 years; women <60 years) cerebral or peripheral vascular disease	
Physical examination	
Tendinous xanthomata	6
Arcus cornealis prior to age 45	4
Cholesterol levels (mm/L)	
LDL-C, >=8.5	8
LDL-C, 6.5-8.4	5
LDL-C, 5.0-6.4	3
DNA Analysis	
Functional mutation in the LDLR, apo B or PCSK9 gene	8
Diagnosis	
Definite familial hypercholesterolaemia Probable familial hypercholesterolaemia Possible familial hypercholesterolaemia Unlikely familial hypercholesterolaemia	>8 points 6-8 points 3-5 points <3 points

Identification and management familial hypercholesterolaemia: what does it mean to primary care?

Nadeem Qureshi, Steve E Humphries, Mary Seed, Philip Rowlands and Rubin Minhas, on behalf of the NICE Guideline Development Group

ABSTRACT

Familial hypercholesterolaemia is one of the most common dominantly inherited disorders to be identified in primary care, leading to raised serum cholesterol evident from the first year of life. Around 1 in 500 people are affected by this condition, but less than 15% of these are currently attending lipid clinics, suggesting that the vast majority are unrecognised in general practice. The recently released National Institute for Health and Clinical Excellence evidence-based guideline on the identification and management of familial hypercholesterolaemia provides an opportunity to bridge this gap. Primary care has a role in systematic and opportunistic case finding, such as recognising the relevance of a family history of

INTRODUCTION

This review summarises the recommendations that have an impact on primary care from the National Institute for Health and Clinical Excellence (NICE) guideline on the identification and management of familial hypercholesterolaemia.* Familial hypercholesterolaemia is an inherited disorder leading to raised serum cholesterol evident from the first year of life. This may present with signs indicative of raised cholesterol levels such as tendon xanthomata, and, if untreated, the development of premature coronary heart disease (CHD). The disorder has an autosomal dominant mode of

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Feasibility of improving identification of familial hypercholesterolaemia in general practice: intervention development study

Nadeem Qureshi,[1] Stephen Weng,[1] Jennifer Tranter,[1] Alia El-Kadiki,[2] Joe Kai[1]

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[1]Division of Primary Care, NIHR School of Primary Care Research, University of Nottingham, Nottingham, UK
[2]Nottingham University Hospitals NHS Trust, Nottingham, UK

Correspondence to
Professor Nadeem Qureshi; nadeem.qureshi@nottingham.ac.uk

ABSTRACT

Objectives: To assess the feasibility of improving identification of familial hypercholesterolaemia (FH) in primary care, and of collecting outcome measures to inform a future trial.

Design: Feasibility intervention study.

Setting: 6 general practices (GPs) in central England.

Participants: 831 eligible patients with elevated cholesterol >7.5 mmol/L were identified, by search of electronic health records, for recruitment to the intervention.

Intervention: Educational session in practice; use of opportunistic computer reminders in consultations or universal postal invitation over 6 months to eligible patients invited to complete a family history questionnaire. Those fulfilling the Simon-Broome criteria for possible FH were invited for GP assessment and referred for specialist definitive diagnosis.

Outcome measures: Rates of recruitment of eligible patients, identification of patients with possible FH, referral to specialist care, diagnosis of confirmed FH in specialist care; and feasibility of collecting relevant outcome measures for a future trial.

Results: Of 173 general practices, 18 were interested in participating and 6 were recruited. From 831 eligible patients, 127 (15.3%) were recruited and completed family history questionnaires: 86 (10.7%) through postal invitation and 41 (4.9%) opportunistically. Among the 127 patients, 32 (25.6%) had a possible diagnosis of FH in primary care. Within 6 months of completing recruitment, 7 patients had had specialist assessment confirming 2 patients with definite FH (28.6%), and 5 patients with possible FH (71.4%). Potential trial outcome measures for lipid tests, statin prescribing and secondary causes of hypercholesterolaemia were extracted using automated data extraction from electronic records alone without recourse to other methods.

Conclusions: The intervention is feasible to implement in GP, and facilitates recruitment of patients with raised cholesterol for targeted assessment and identification of FH. Extracting data directly from electronic records could be used to evaluate relevant outcome measures in a future trial.

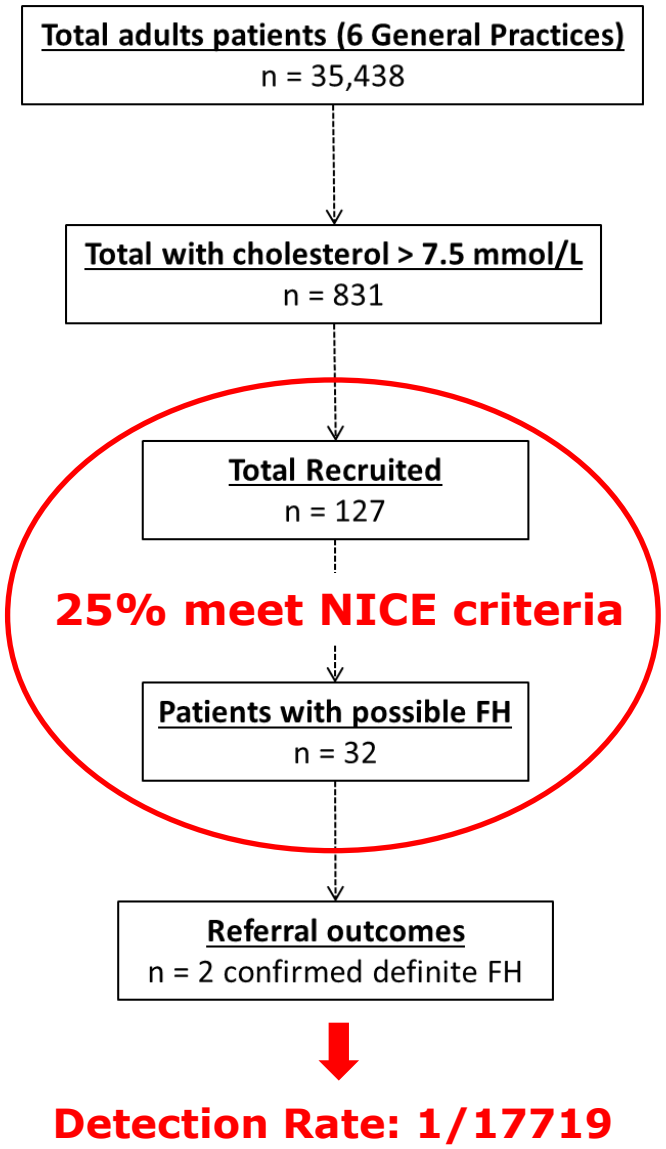
Strengths and limitations of this study

- This feasibility study was able to engage general practices (GPs) and patients from underserved populations in an intervention to identify familial hypercholesterolaemia (FH) more systematically.
- Extraction of data using automated GP computer searches can capture important outcome measures for a future trial of FH identification.
- Further strategies are needed if engaging eligible patients is to be improved on opportunistic contact during GP consultations.
- The 6-month patient follow-up period used was too short to elicit complete data on all relevant outcome measures, such as eventual specialist assessment.

INTRODUCTION

Familial hypercholesterolaemia (FH) is one of the most common inherited autosomal dominant disorders and is associated with elevated low-density lipoprotein cholesterol levels. In the UK, around 1 in 500 to 1 in 200 people are affected by the heterozygote form of this condition.[1] Left untreated this can lead to premature coronary heart disease in those individuals affected.[2 3] However, with appropriate lipid-lowering treatment, intervention is highly effective and life expectancy can return to normal.[4]

Despite the overwhelming case for treatment and national guidelines recommending early identification, it is estimated that up to 80% of heterozygote FH still remain unrecognised.[5 6] Of most concern, individuals with raised cholesterol levels documented in general practice (GP) medical records may not be recognised to have possible FH. However, primary care is an ideal setting to identify possible FH cases through identification of those with raised cholesterol and relevant family histories. Current UK National Institute for Health and Care Excellence



Research question: Can we improve identification of FH in primary care using a novel case-finding approach and how does this compare to using existing criteria for case-finding?

Aim: To develop and validate a bespoke case-finding tool using only data routinely available in primary care electronic health records, and compare this to existing criteria

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Improving identification of Familial Hypercholesterolaemia in Primary Care

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Improving identification of familial hypercholesterolaemia in primary care: Derivation and validation of the familial hypercholesterolaemia case ascertainment tool (FAMCAT)

Stephen F. Weng [a], Joe Kai [a], H. Andrew Neil [b], Steve E. Humphries [c], Nadeem Qureshi [a,*]

[a] Division of Primary Care, School of Medicine, University of Nottingham, UK
[b] Wolfson College, University of Oxford, UK
[c] Centre for Cardiovascular Genetics, Institute of Cardiovascular Science, University College London, UK

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ABSTRACT

Objective: Heterozygous familial hypercholesterolaemia (FH) is a common autosomal dominant disorder. The vast majority of affected individuals remain undiagnosed, resulting in lost opportunities for preventing premature heart disease. Better use of routine primary care data offers an opportunity to enhance detection. We sought to develop a new predictive algorithm for improving identification of individuals in primary care who could be prioritised for further clinical assessment using established diagnostic criteria.

Methods: Data were analysed for 2,975,281 patients with total or LDL-cholesterol measurement from 1 Jan 1999 to 31 August 2013 using the Clinical Practice Research Datalink (CPRD). Included in this cohort study were 5050 documented cases of FH. Stepwise logistic regression was used to derive optimal multivariate prediction models. Model performance was assessed by its discriminatory accuracy (area under receiver operating curve [AUC]).

Results: The FH prediction model (FAMCAT), consisting of nine diagnostic variables, showed high discrimination (AUC 0.860, 95% CI 0.848–0.871) for distinguishing cases from non-cases. Sensitivity analysis demonstrated no significant drop in discrimination (AUC 0.858, 95% CI 0.845–0.869) after excluding secondary causes of hypercholesterolaemia. Removing family history variables reduced discrimination (AUC 0.820, 95% CI 0.807–0.834), while incorporating more comprehensive family history recording of myocardial infraction significantly improved discrimination (AUC 0.894, 95% CI 0.884–0.904).

Conclusion: This approach offers the opportunity to enhance detection of FH in primary care by identifying individuals with greatest probability of having the condition. Such cases can be prioritised for further clinical assessment, appropriate referral and treatment to prevent premature heart disease.

1. Introduction

Familial hypercholesterolaemia (FH) is the commonest autosomal dominant disorder, with between 1/200 to 1/500 individuals having the heterozygote form [1]. This genetic disorder is characterized by high serum cholesterol concentrations and is caused by mutations of the *LDLR* gene [1]. Without treatment, young adults aged 20 to 39 years with heterozygous FH are estimated to have nearly a 100-fold increase in mortality risk from CHD compared to unaffected adults [2,3]. Evidence indicates FH patients have up to a 37% reduction in CHD mortality following treatment with statins and improved life expectancy, emphasizing the major benefit of early identification and treatment [4]. If such patients are not recognized in primary care, they will be treated like other patients with common multifactorial causes for raised cholesterol and prescribed lower potency statins, or offered no medication at all if their global cardiovascular risk score is not elevated.

In the UK, the National Institute for Health and Care Excellence (NICE) recommends the Simon-Broome Register criteria [3] which includes cholesterol concentrations, clinical characteristics such as

* Corresponding author. Address: 1309 Tower, University Park, Nottingham NG7 2RD, UK.
E-mail address: nadeem.qureshi@nottingham.ac.uk (N. Qureshi).

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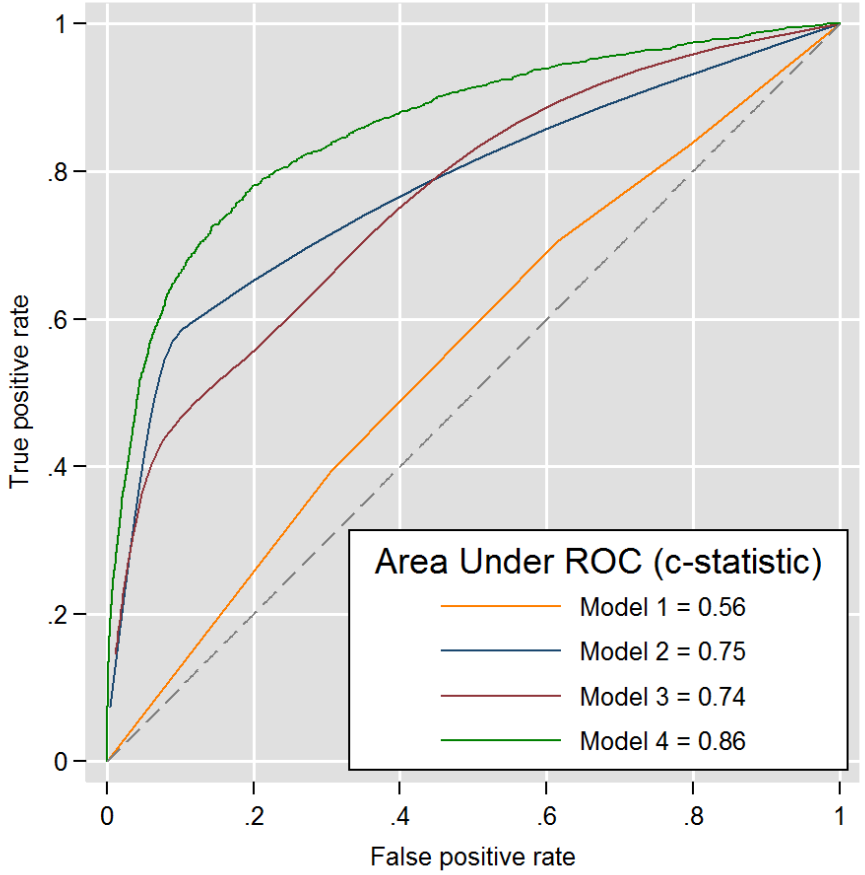
Diagnostic variables indicating probability of FH

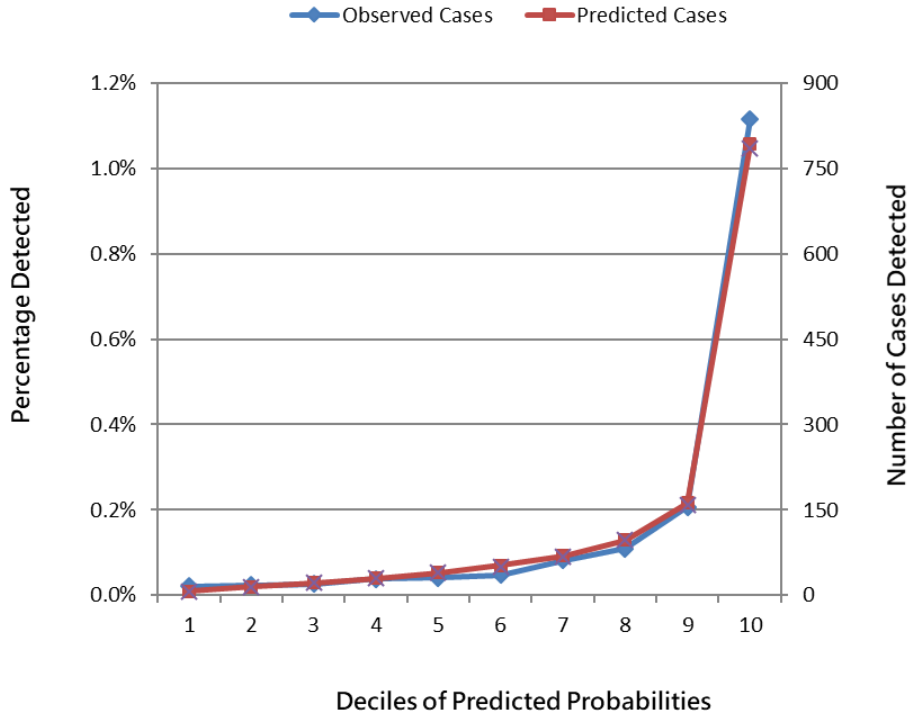
- Highest Total Cholesterol (mmol/L)*
- Highest LDL Cholesterol (mmol/L)*
- Age during cholesterol measurement
- Triglycerides during cholesterol measurement (mmol/L)
- Treatment with lipid lowering drugs during cholesterol measurement
- Previous history of coronary heart disease < 60 years
- Family history of myocardial infarction*
- Family history of raised cholesterol*
- Family history of familial hypercholesterolaemia
- Liver disease
- Diabetes
- Hypothyroidism
- Chronic kidney disease

**apriori:* Included in NICE Simon-Broome diagnosis criteria for possible familial hypercholesterolaemia

Familial Hypercholesterolaemia Case Ascertainment Tool (FAMCAT)



FAMCAT Calibration Plot



Model 1: Total cholesterol > 7.5 mmol/L or LDL cholesterol > 4.9 mmol/L
Model 2: Simon Broome criteria
Model 3: Dutch Lipid Clinic criteria
Model 4: FAMCAT model

Familial Hypercholesterolaemia Case Ascertainment Tool (FAMCAT)

Subsequent External Validation Studies (2017-2018)

- NIHR SPCR Funding to conduct two external validations of FAMCAT in other GP systems

CPRD →

681 General Practices using Vision GP systems
Algorithm derivation: **2,228,562 patients**
Internal validation: **742,851 patients** (randomly selected)

QRESEARCH →

1500 General Practices using EMIS GP systems
External validation: **747,000 patients** (randomly selected)

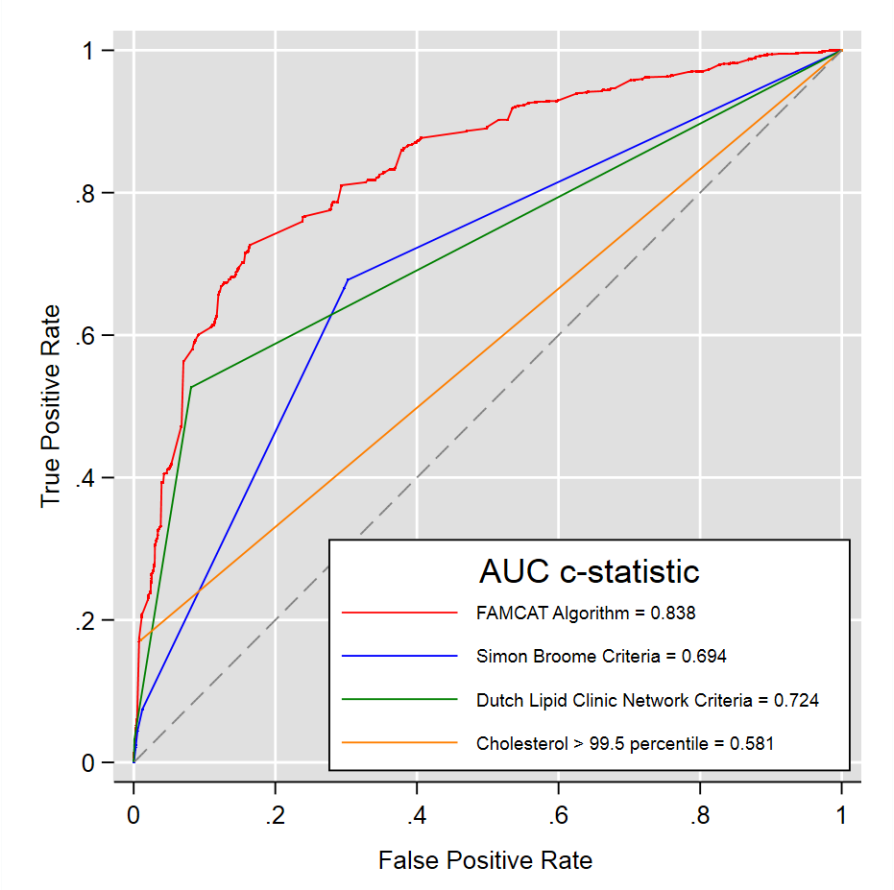
RCGP Royal College of General Practitioners →

260 General Practices using EMIS/TPP GP systems
External validation: **1,030,183 patients** (entire sample)

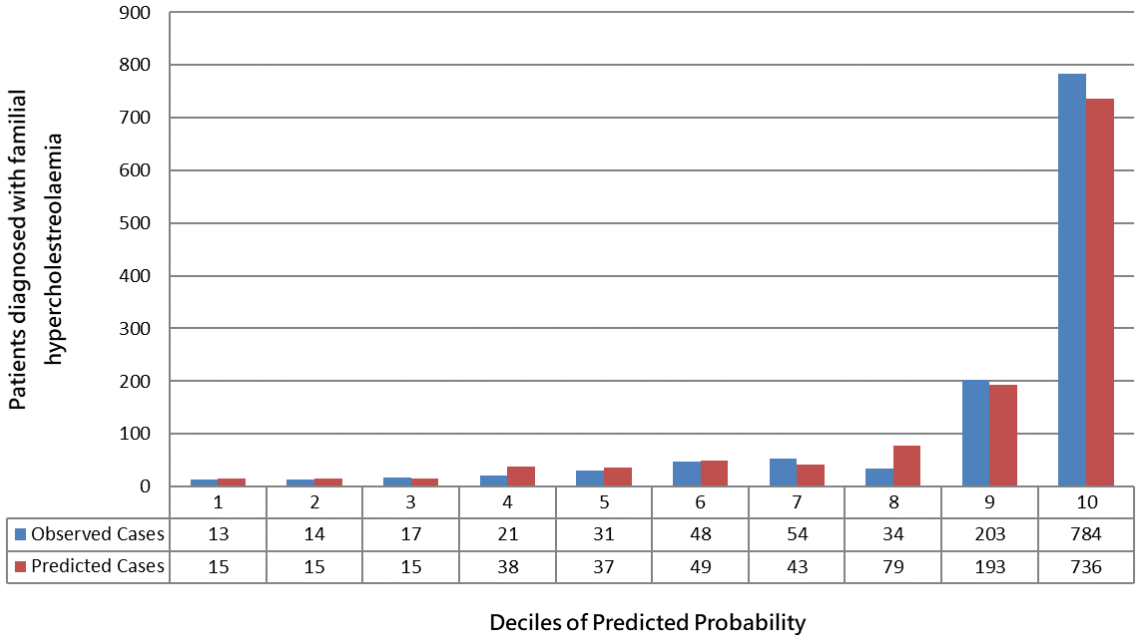
Familial Hypercholesterolaemia Case Ascertainment Tool (FAMCAT)

QRESEARCH External Validation

Area under curve



FAMCAT Calibration Across Deciles



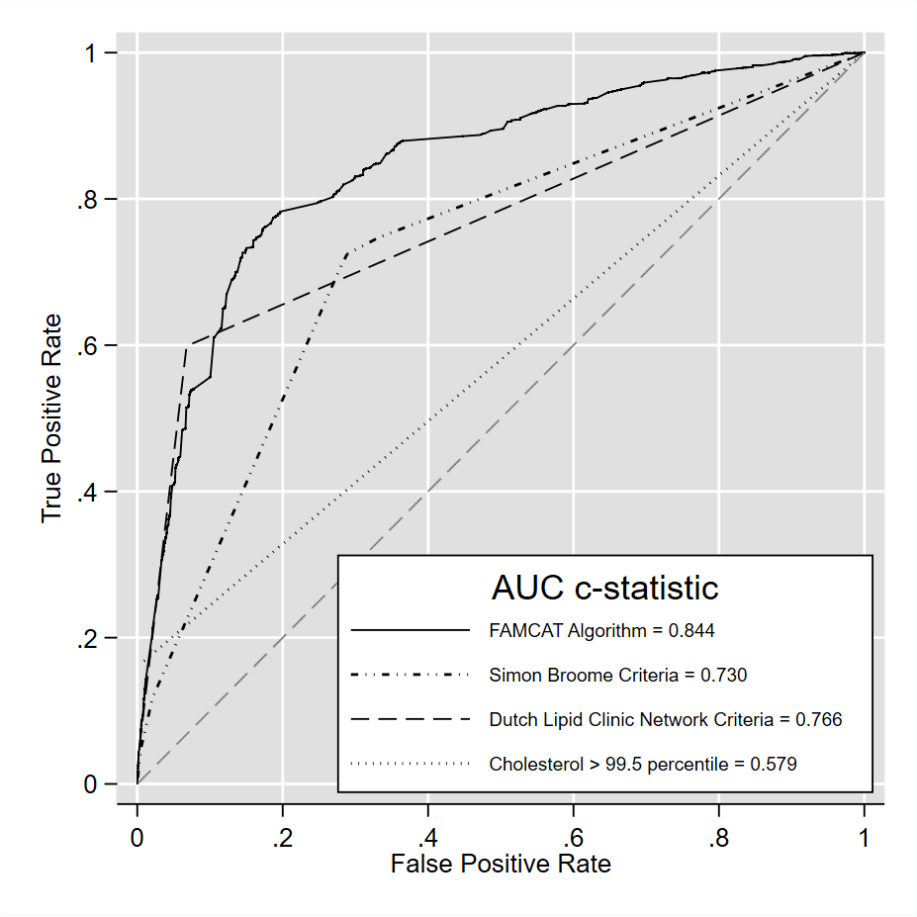
	1	2	3	4	5	6	7	8	9	10
Observed Cases	13	14	17	21	31	48	54	34	203	784
Predicted Cases	15	15	15	38	37	49	43	79	193	736

S. Weng, J. Kai, R. Akyea, N. Qureshi. Improving identification of familial hypercholesterolaemia in primary care using FAMCAT (Familial Hypercholesterolaemia Case Ascertainment Tool): validation in a large population database. **European Society for Human Genetics Conference** in Milan, Italy *16-18 June 2018*

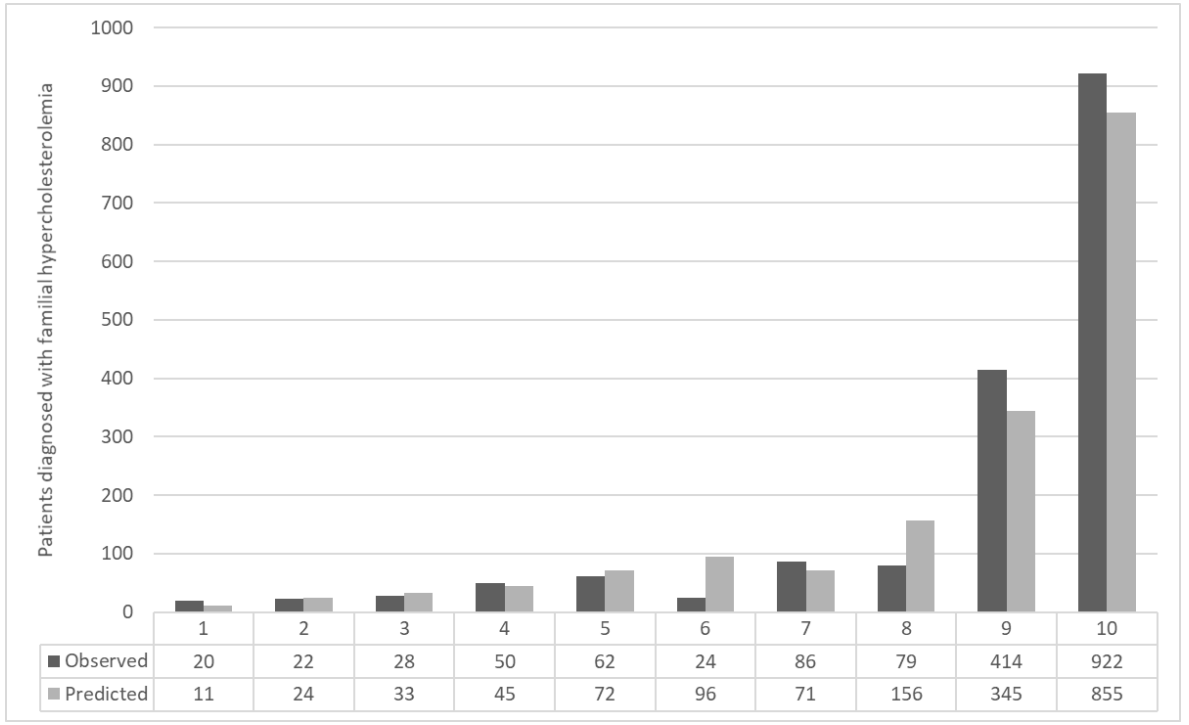
Familial Hypercholesterolaemia Case Ascertainment Tool (FAMCAT)

RCGP External Validation

Area under curve



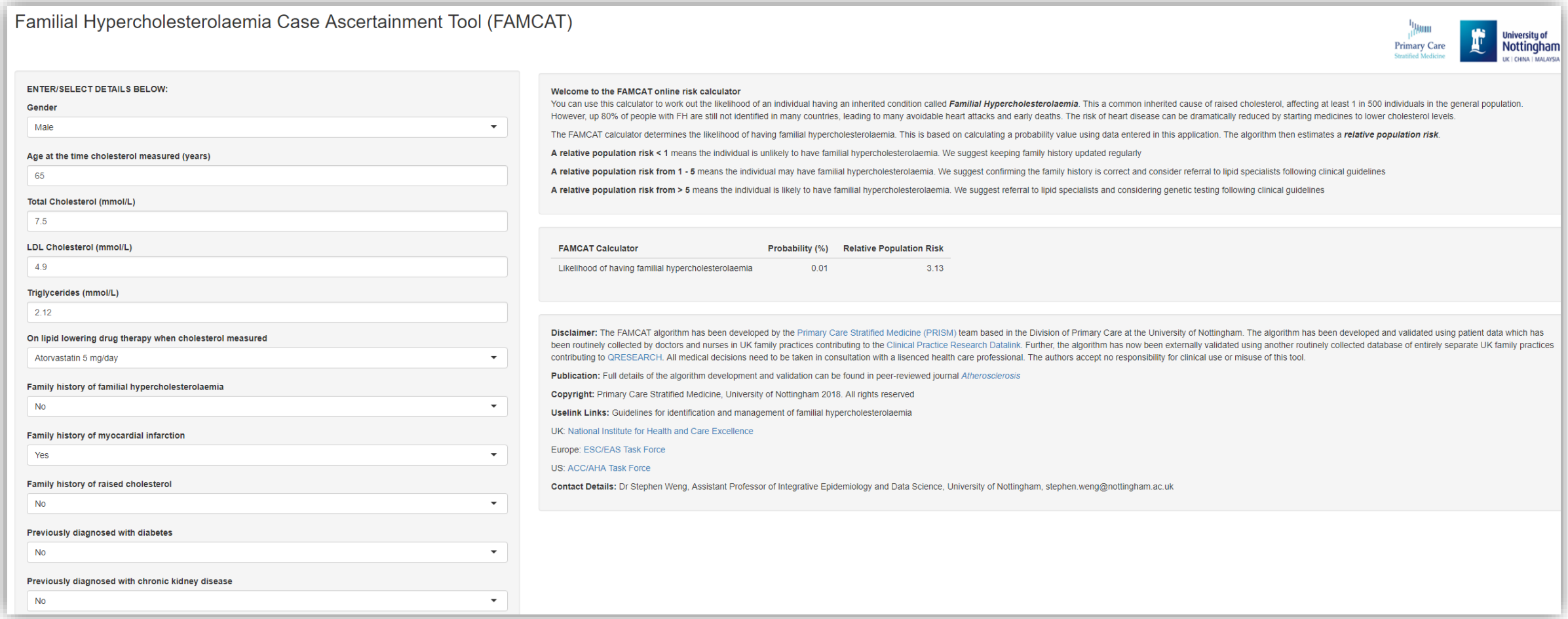
FAMCAT Calibration Across Deciles



	1	2	3	4	5	6	7	8	9	10
Observed	20	22	28	50	62	24	86	79	414	922
Predicted	11	24	33	45	72	96	71	156	345	855

Familial Hypercholesterolaemia Case Ascertainment Tool (FAMCAT)

FAMCAT web-based calculator



https://prism-uon.shinyapps.io/FAMCAT/

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Familial Hypercholesterolaemia Case Ascertainment Tool (FAMCAT)

quick guide

Familial Hypercholesterolaemia

Background

Around 80-90% of familial hypercholesterolaemia (FH) cases remain undiagnosed. If left untreated, about 50% of men and 30% of women with FH will develop coronary heart disease before they are 55[1]. Early identification and effective treatment of FH patients can help to ensure normal life expectancy.

This quality improvement tool helps GP practices to case find patients who may have FH but also may be missing a coded diagnosis. The tool will also identify those at greatest risk of developing the disease (ranked in order of likelihood), so that they can be monitored or reviewed. Additionally, any patients who are currently untreated will be highlighted for review and, through use of the tool, practices can optimise lipid lowering treatment regimes for all patients with the disease.

The FH quality improvement tool uses the CHART analysis software which presents data at both practice and patient levels. Users can quickly drill down to examine detailed patient care within a comprehensive datasheet and produce patient lists quickly and easily. CHART also provides the ability to create mail merge lists for patient recall invitation letters and is compatible for use with all GP clinical systems.

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0115 846 6420
www.nottingham.ac.uk/primis

The Familial Hypercholesterolaemia quality improvement tool can help practices by:

- generating a list of patients who may have FH but who do not have a coded diagnosis
- identifying patients who are at increased risk of developing FH and categorising them by level of risk (using the FAMCAT algorithm)
- offering a comparative analysis service via CHART Online, which enables comparison with other practices, locally or nationally
- establishing a more accurate prevalence rate for FH within the practice population
- highlighting patients with the disease who are currently untreated
- highlighting recording rates of important family history information

- identifying opportunities to optimise lipid lowering treatment regimes for all patients with the disease
- contributing to the delivery of the NHS Outcomes Framework and the Clinical Commissioning Group Outcomes Indicator Set
- providing a mail merge function to generate letters to send to high risk patients about collecting their family history
- providing data in a format for appraisal and revalidation and providing a method for GPs to reflect on their clinical practice

PRIMIS

Date of issue: January 2017

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FH management - CHART summary report

The FH quality improvement tool displays the results as an interactive practice level summary.

Users can quickly drill through the summary report to access detailed patient level data and pre-filtered patients lists.

Summary sheet

The summary sheet includes a range of data tables offering an instant view of practice level data:

	Diagnosed	Very High Risk	High Risk	Population Risk
BREAKDOWN OF ABOVE PATIENTS INTO RISK GROUPS	8	82	491	4149
Of whom were diagnosed inlast 12 months	2			
Of whom have been screened in last 12 months	0	2	4	17
Of whom have not been screened in last 12 months	6	80	487	4132

	Diagnosed	Very High Risk	High Risk	Population Risk
LIPID LOWERING DRUGS IN LAST 6 MONTHS				
All patients	8	82	491	4149
Of whom have a contraindication to statins	0	0	1	8
Of whom are on high potency statins	4	26	170	870
Of whom are on medium potency statins	1	0	8	43
Of whom are on low potency statins	0	1	0	9
Of whom are on another lipid lowering drug	0	2	0	6
Of whom have no statin contraindication and are not on any of the above drugs	3	53	312	3213

About this quality improvement tool

The PRIMIS Familial Hypercholesterolaemia quality improvement tool was developed in collboration with the Applied Genetics and Ethnicity research group at The University of Notttingham. This tool is based on the FAMCAT algorithm[2] developed by academics in the Applied Genetics and Ethnicity research group.

Footnotes

[1] Youngblom E, Knowles JW. Familial Hypercholesterolemia. 2014 Jan 2. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2015. Available from: http://www.ncbi.nlm.nih.gov/books/NBK174884/ Accessed January 6th, 2017

[2] Weng SF, Kai J, Neil HA, Humphries SE, Qureshi N. Improving identification of familial hypercholesterolaemia in primary care: Derivation and validation of the familial hypercholesterolaemia case ascertainment tool (FAMCAT). Atherosclerosis 2015; 238(2):336-43 doi:10.1016/j.atherosclerosis.2014.12.034.

PRIMIS
Familial Hypercholesterolaemia

Use of the FH quality improvement tool is FREE to practices registered with the PRIMIS Hub membership service.

Basic membership is also free of charge and includes access to several other PRIMIS products, including the GRASP suite of tools and both the CHART and CHART Online software tools. Sign up for free basic PRIMIS Hub membership and find out about other options at:

nottingham.ac.uk/primis/joinus

Five key actions following use of the FH quality improvement tool

Review any patients at very high risk of developing FH who have not had recent screening

Click through the summary sheet to access this patient list. The inbuilt mail merge function can also assist with generating invitation letters.

Review any patients with FH who have not had recent screening

Patients with a coded diagnosis of FH who have not had screening in the last 12 months may also benefit from review to ensure they are on the best treatment.

Improve recording of important family history information through systematic collection

Patients classified as being at high risk of FH who do not have a family history recorded should be encouraged to collect systematic family history. High risk patients may well become very high risk once an accurate family history has been recorded (and this is positive). The mail merge function can assist with generating letters to send to these high risk patients about collecting their family history.

Assess current treatment regimes

Review the type and dosage of lipid lowering therapy for patients who are diagnosed with FH. If diagnosed patients are not currently being treated (and are not contraindicated), consider commencement of lipid lowering medication.

Review coding standards within the practice

Use the information provided with the report to assess the accuracy of coding, particularly in relation to confirming FH diagnoses, drug allergies and contraindications and important family history codes. Consider the reasons why any data items are missing and how to prevent recurrence for other patients.

PRIMIS' development of this tool was part supported by independent funding from Amgen.

AMGEN

PRIMIS audit tools are designed to signpost practices to patients who may be of interest and/or concern and not to replace clinical decision making.

The FH quality improvement tool works with CHART and CHART Online.

https://www.nottingham.ac.uk/primis/tools-audits/tools-audits/familial-hypercholesterolaemia.aspx

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FHC CASEFINDER LIBRARY

Practice Population	5330
Of whom are aged 16 to 120	4630
Of whom have had a cholesterol recording at any time	1269

BREAK DOWN OF ABOVE PATIENTS INTO RISK GROUPS	Diagnosed	Very High Risk	High Risk	Population Risk
Of whom were diagnosed in last 12 months	0			
Of whom have been screened in last 12 months	0	0	0	0
Of whom have not been screened in last 12 months	2	11	97	1159

PATIENTS SCREENED IN LAST 12 MONTHS	Diagnosed	Very High Risk	High Risk	Population Risk
Number of patients screened/assessed/in last 12 months	0	0	0	0
Screening Methods				
Of whom were assessed by Dutch Criteria in last 12 months	0	0	0	0
Of whom were assessed by Simon Broome in last 12 months	0	0	0	0
Of whom had Hyperlipidaemia screen in last 12 months	0	0	0	0
Referred to Specialist or Consultant				
Of whom were referred to a Specialist/Consultant in last 12 months	0	0	0	0

FAMILY HISTORY CODES - Recorded since July 2016	Diagnosed	Very High Risk	High Risk	Population Risk
All patients	2	11	97	1159
Of whom have a Negative Family History	0	0	0	0
Of whom have a Positive Family History	0	0	0	0
Of whom have a Unknown Family History	2	11	97	1159
Of whom have a Contradictory Family History	0	0	0	0

LIPID LOWERING DRUGS IN LAST 6 MONTHS	Diagnosed	Very High Risk	High Risk	Population Risk
All patients	2	11	97	1159
Of whom have a contraindication to statins	0	0	0	2
Of whom are on high potency statins	0	0	0	0
Of whom are on medium potency statins	0	0	0	0
Of whom are on low potency statins	0	0	0	0
Of whom are on another lipid lowering drug	0	0	0	0
Of whom have no statin contraindication and are not on any of the above	2	11	97	1157

Diagnosis and Screening

Diagnosed	Very High Risk	High Risk	Population Risk
2	11	97	1159
0			
0	0	0	0
2	11	97	1159

Family History Recording

Diagnosed	Very High Risk	High Risk	Population Risk
2	11	97	1159
0	0	0	0
0	0	0	0
2	11	97	1159
0	0	0	0

Drug Prescribing

Diagnosed	Very High Risk	High Risk	Population Risk
2	11	97	1159
0	0	0	2
0	0	0	0
0	0	0	0
0	0	0	0
0	0	0	0
2	11	97	1157

Sample Patient Data From General Practice

MIQUEST response file FHCRREPA.CSV was created on 24/03/16 using Refdate 22/03/16
FHCRISKSCORE-ALG2 FHCRREPA: FHC Risk Score - Pseudonymised

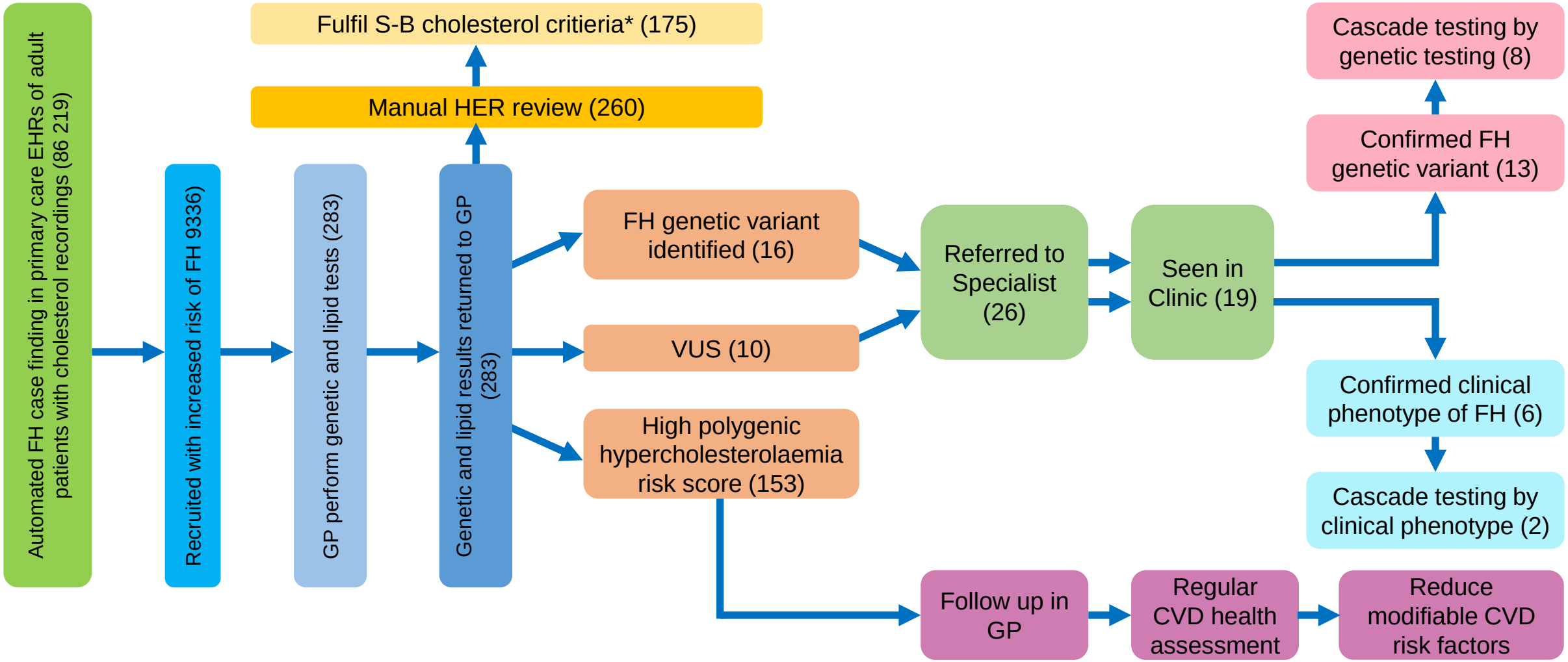
Reference	Age	Sex	Registered_Date	SEX CATEGORY	Relative Risk of FH	Latest TC Ever Code	Latest TC Ever Date	Latest TC Value Ever	Latest TC Category	Latest LDL Ever Code	Latest LDL Ever Date	Latest LDL Ever Value1	Latest LDL Category	Item to use	TC/LDL CATEGORY	TC/LDL AGE	Latest TC with a High Potency LLD	Latest TC with a High Potency LLD	Latest High Potency LLD with a TC	Latest High Potency LLD with a TC	Latest TC with a Med Potency LLD
15FAEE03	43	M	08/04/11	1	42.17656	44P	26/07/15	7.80	4	44P6	26/07/15	5.10	4	TC	4	42					
F7B538D4	68	F	12/03/91	2	31.18372	44P	07/01/16	7.40	3	44P6	07/01/16	5.10	4	LDL	4	68	44P	07/01/16	bxe7	03/12/15	
3E2BBD5A	70	F	04/12/08	2	29.6927	44P	28/04/15	7.60	4	44P6	28/04/15	4.80	3	TC	4	69	44P	28/04/15	bxi1	03/03/15	
BE0C13A2	44	M	20/10/15	1	16.313	44P	07/05/15	8.50	4	44P6	07/05/15	5.90	4	TC	4	43					
BBF90797	33	M	13/10/15	1	14.65782	44P	28/11/15	6.80	3	44P6	28/11/15	4.70	3	TC	3	33					
B7BF3ADA	54	M	29/03/01	1	14.42518	44P	22/07/08	6.20	2	44P6	22/07/08	4.50	3	LDL	3	46	44P	22/07/08	bxi2	18/07/08	
41C455DB	45	F	30/10/12	2	14.09723	44P	31/03/15	7.90	4	44P6	31/03/15	5.70	4	TC	4	44					
0615AE0B	43	M	24/04/07	1	12.71762	44P	09/04/15	7.30	3	44P6	09/04/15	5.40	4	LDL	4	42					
2F521C20	53	M	01/09/14	1	11.97708	44P	03/03/16	2.70	1	44P6	03/03/16	1.30	1	TC	1	53	44P	03/03/16	bxi2	19/02/16	
88D0C573	46	M	21/07/09	1	11.53054	44P	18/03/14	7.10	3	44P6	18/03/14	5.00	4	LDL	4	44					
6A9F857E	35	M	29/03/11	1	11.22341	44P	26/04/13	6.00	2	44P6	26/04/13	5.10	4	LDL	4	32					
8A95DB4C	51	F	20/02/07	2	11.18979	44P	04/09/12	7.60	4	44P6	04/09/12	4.50	3	TC	4	47					
6956D3D9	52	F	02/09/97	2	11.03425	44P	01/10/12	8.40	4	44P6	01/10/12	4.70	3	TC	4	49					
33C6EB5D	36	M	06/08/13	1	10.1758	44P	31/10/13	7.20	3	44P6	31/10/13	5.30	4	LDL	4	34					
D4E774DC	31	M	31/12/07	1	9.924582	44P	25/11/14	5.20	2	44P6	25/11/14	3.10	1	TC	2	30	44P	25/11/14	bxi3	25/11/14	
3A95FA8F	56	M	24/07/12	1	9.281483	44P	25/02/15	6.30	2	44P6	25/02/15	4.70	3	LDL	3	55	44P	25/02/15	bxi2	19/02/15	
115DD77E	54	M	01/07/10	1	9.02523	44P	11/01/11	7.10	3	44P6	11/01/11	5.10	4	LDL	4	49					
B8BE6AF5	31	M	05/08/13	1	8.855387	44P	23/02/16	8.80	4	44P6	23/02/16	6.60	4	TC	4	31					
879CB1AC	55	F	01/10/98	2	8.636773	44P	23/04/15	8.00	4	44P6	23/04/15	5.20	4	TC	4	54					
275086EC	52	M	01/05/14	1	8.5937	44P	09/09/14	7.10	3	44P6	09/09/14	5.10	4	LDL	4	50					
BB2CE4FD	55	M	10/12/13	1	7.419001	44P	20/12/13	6.80	3	44P6	20/12/13	5.10	4	LDL	4	53					
836EB5AB	49	M	17/06/99	1	7.178194	44P	12/05/15	6.90	3	44P6	12/05/15	3.60	2	TC	3	48					
39D35641	41	F	24/09/14	2	7.085494	44P	04/11/14	7.66	4					TC	4	40					
8886E230	45	M	11/08/04	1	6.753455	44P	22/05/15	6.00	2	44P6	22/05/15	4.10	2	TC	2	44					
551F51DD	41	F	19/10/99	2	6.746709	44P	22/09/15	8.18	4	44P6	07/07/15	5.30	4	TC	4	41					
4AAB8BD5	58	M	29/03/00	1	6.495169	44P	19/01/12	7.50	3	44P6	19/01/12	5.30	4	LDL	4	54	44P	05/05/10	bxd5	04/05/10	44P

Age	Sex	Registered_Date	SEX CATEGORY	Relative Risk of FH
43	M	08/04/11	1	42.17656
68	F	12/03/91	2	31.18372
70	F	04/12/08	2	29.6927
44	M	20/10/15	1	16.313
33	M	13/10/15	1	14.65782
54	M	29/03/01	1	14.42518
45	F	30/10/12	2	14.09723
43	M	24/04/07	1	12.71762
53	M	01/09/14	1	11.97708
46	M	21/07/09	1	11.53054

Patients ranked highest to lowest probability of FH (note yellow highlight: FAMCAT captures high number of younger patients (< 50) with raised cholesterols) → these are the priority cases to be assessed

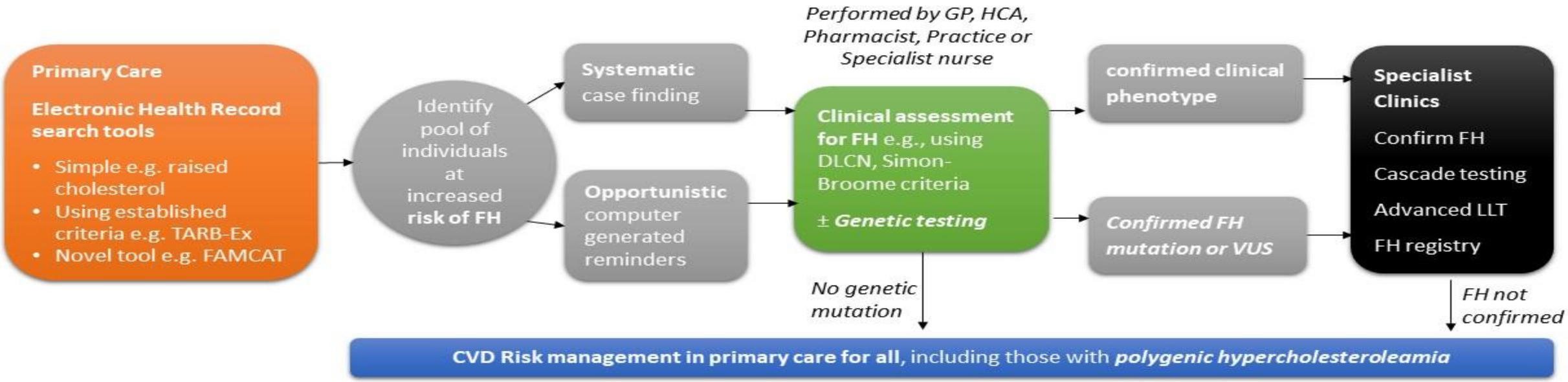
University of Nottingham
UK | CHINA | MALAYSIA

FAMCAT & Genetic testing clinical utility study



Qureshi N, et al. Case-finding and genetic testing for familial hypercholesterolaemia in primary care Heart 2021;0:1–6. doi:10.1136/heartjnl-2021-319742

Implementation of FH identification & Genetic testing in PC



Qureshi N , Patel RS . Hiding in plain sight: supporting primary care to find familial hypercholesterolaemia and save lives. *Heart* 2021;107:1190–2. doi:10.1136/heartjnl-2021-319266

05 Q&A round up

Next steps:

Join us for an informal case based interactive clinic on FH: Weds 3rd Nov 1-2pm

Join us for the next webinars:

Mon 15th November 1-2pm: Diet and Behaviour change

Behavioural change online and **Lynne Garton,** Dietetic Advisor HEARTUK

Weds 24th November 12-1pm: Post Cardiovascular disease event management

Dr Rani Katib Consultant Pharmacist in Cardiology and Cardiovascular Research. Leeds Institute of Cardiovascular and Metabolic Medicine
Dr Marc Bailey Associate Professor of Vascular Medicine & BHF Intermediate Clinical Research Fellow. Honorary Senior Clinical Lecturer in Vascular Surgery
Professor Stephen Wheatcroft interventional cardiologist and vascular biologist Leeds NHS Trust and University of Leeds

All programme content, recordings and next webinar bookings will be housed in the HEART UK pages. Visit the site for the new e-Learning modules on Identifying FH in primary care**,** Statin Intolerance, and the Lipid Management Pathway

Lowering Cholesterol.

Saving Lives.

TheAHSNNetwork ACCELERATED ACCESS COLLABORATIVE HEART UK THE CHOLESTEROL CHARITY NHS

Tackling Cholesterol Together

Thank you

This webinar has now finished.

Today's slides and recording will be available after the webinar on the HEART UK pages. Visit the site for the **new** e-Learning modules Identifying FH in primary care, Statin Intolerance, and the Lipid Management Pathway

All programme content, recordings and next webinar bookings will be housed here: https://www.heartuk.org.uk/tackling-cholesterol-together/home

Some content in this deck is based on slides created and provided by Amgen UK in scientific exchange to our speakers, which have been adapted for this talk