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Update on FH Services and Management in Wales

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FH WALES

Familial Hypercholesterolaemia

Declarations of Interest

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- Sanofi, Daiichi Sankyo, Amgen

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Introduction

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Aim – To provide an overview of the management of familial hypercholesterolaemia in Wales.

- Describe the incidence and burden of familial hypercholesterolemia in Wales and the UK
- Describe the optimum approach to the management of familial hypercholesterolemia, referring to national and international guidelines
- Provide an overview of the All Wales Familial Hypercholesterolaemia Service and the impact this has had on patient care

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Acknowledgements – All Colleagues; especially Kate Haralambos (All Wales Network Manager) for providing FH / Genotype data.

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Familial Hypercholesterolaemia

Missed Opportunity??

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Fit / athletic looking 41yo ♂ self presented to A&E:

- Mother lives outside Wales – apparently with clinical diagnosis of FH (family never screened)
- Diagnosing and treating people with FH and 'cascade' screening their families provides an opportunity for preventing the damage caused by coronary heart disease

Laboratory number: 800079168006
Clinical information: Ant STEMI
Result/Report origin: Glan Clwyd Hospital: Blood Sciences

C-reactive protein (CRP) (AUTHORISED [A])

C-reactive protein (CRP)	**32**	**mg/L**	**H <5**

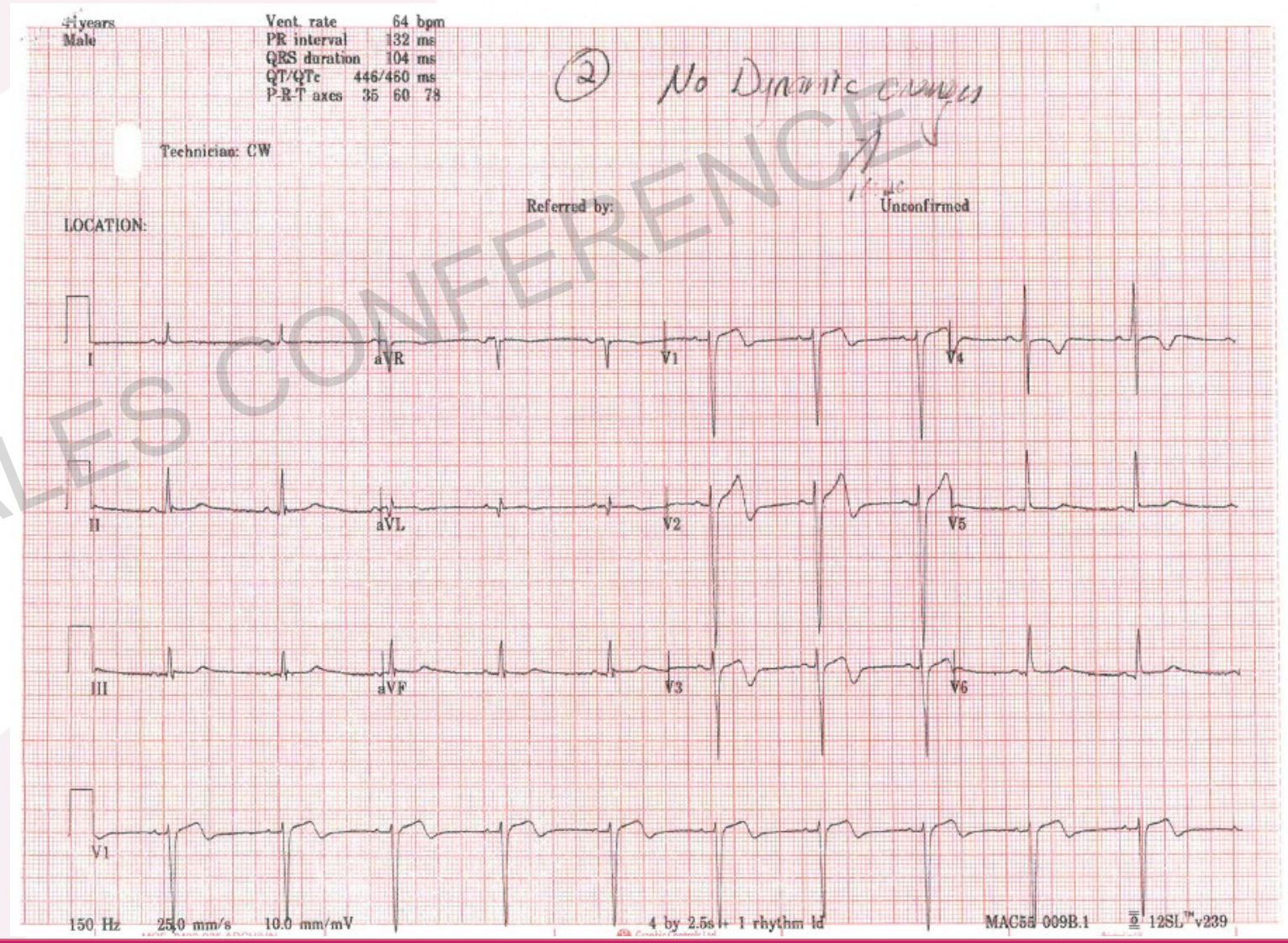
Cardiac Troponin T (AUTHORISED [A])

Cardiac Troponin T	260	ng/L	
Previous Troponin T	329	ng/L	
%age difference	-21.0	%	
Time span (Troponin)	5.8	Hours	

Change of 20-100% in cTnT-hs - ?significant change. Further evaluation may be needed to determine if acute or chronic cause.

Lipid profile (AUTHORISED [A])

Cholesterol	8.7	mmol/L	
Triglyceride	1.2	mmol/L	<2.0
HDL Cholesterol	1.1	mmol/L	>1.0
Non HDL Cholesterol	7.6	mmol/L	
Cholesterol:HDL ratio	7.9	ratio	
LDL Cholesterol	7.1	mmol/L	



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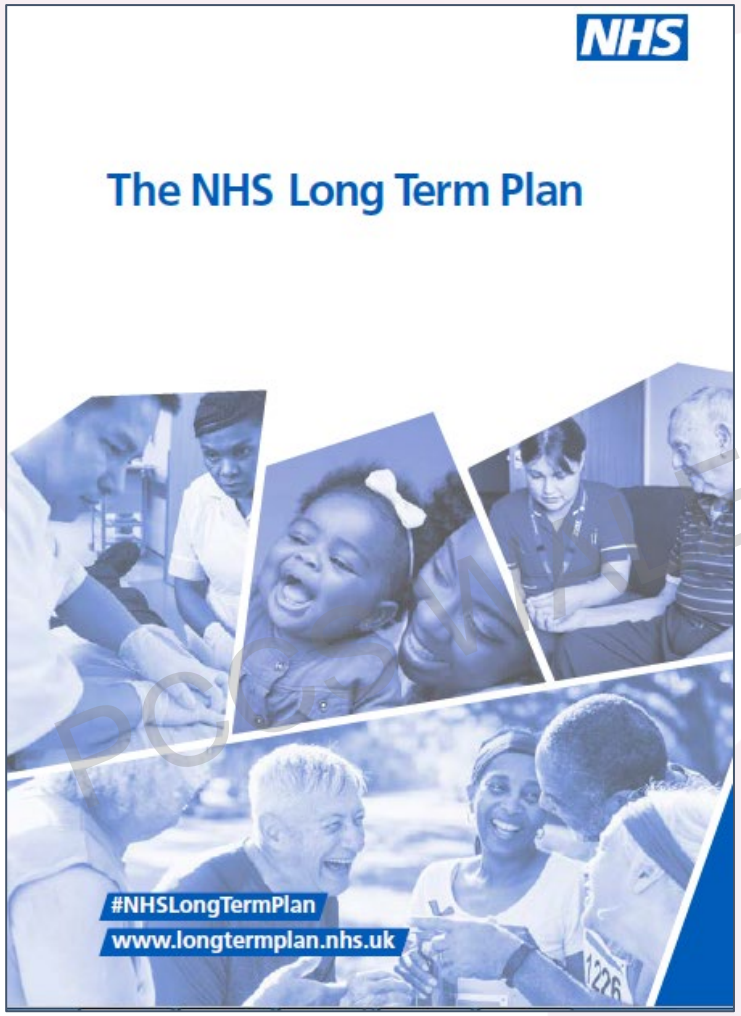
A&E, accident & emergency; FH, familial hypercholesterolaemia; yo, year old. Public Health England. Familial Hypercholesterolaemia: Implementing a systems approach to detection and management. Available from https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/731873/familial_hypercholesterolaemia_implementation_guide.pdf. Accessed March 2023

NHS Long Term Plan



- Commitments set out in the NHS Long Term Plan to improve detection and management of atrial fibrillation, high blood pressure and high cholesterol in order to prevent heart attacks and strokes
- Priority areas include; identification and optimal management of patients with high risk conditions for CVD (AF, hypertension, high cholesterol, diabetes - **A B C D**)
- CVD – recognised as the single biggest area where the NHS can safe lives over next 10 years

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AF, atrial fibrillation; CVD, cardiovascular disease; NHS, National Health Service. NHS. The NHS Long Term Plan. Available from https://www.longtermplan.nhs.uk/wp-content/uploads/2019/08/nhs-long-term-plan-version-1.2.pdf. Accessed March 2022

NHS Long Term Plan...FH!

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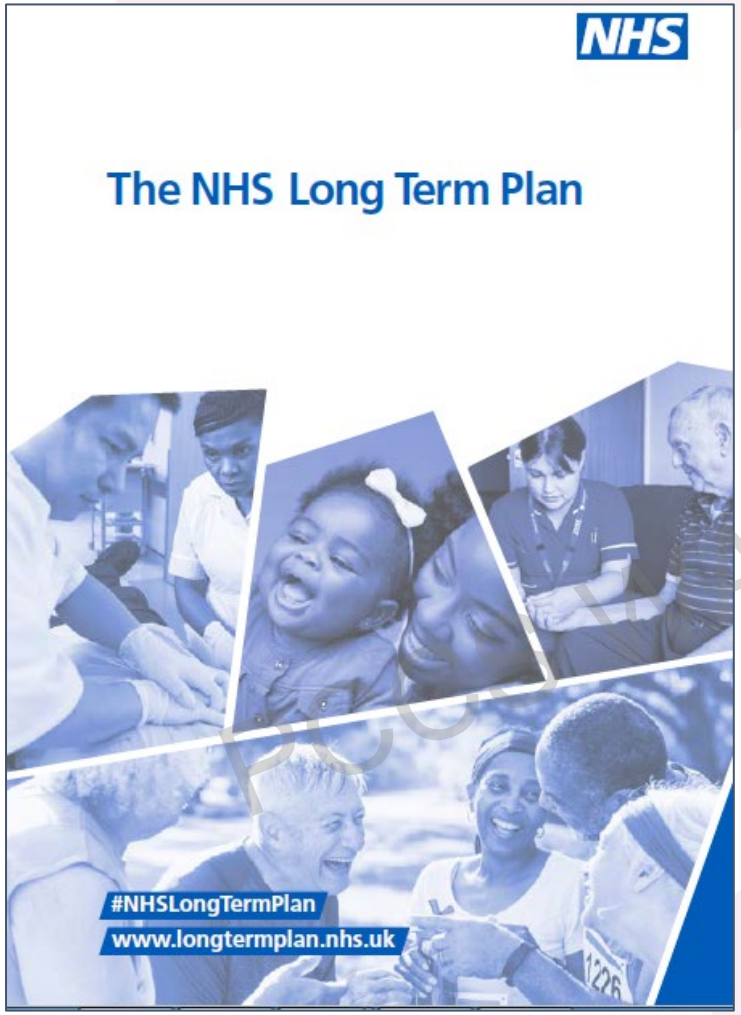

Focus targeted investment in areas of transformative innovation - particularly genomics

More personalised therapeutic options:

- "Expanding access to genetic testing for Familial Hypercholesterolaemia (FH), which causes early heart attacks and affects at least 150,000 people in England, will enable us to diagnose and treat those at genetic risk of sudden cardiac death."
- "Currently only 7% of those with FH have been identified. Aim to improve that to at least 25% in the next five years **(2024)** through the NHS genomics programme."

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FH, familial hypercholesterolaemia; NHS, National Health Service. NHS. The NHS Long Term Plan. Available from https://www.longtermplan.nhs.uk/wp-content/uploads/2019/08/nhs-long-term-plan-version-1.2.pdf. Accessed March 2022

Most FH due to LDLR Variants…

And ~5% by APOB, 2% PCSK9

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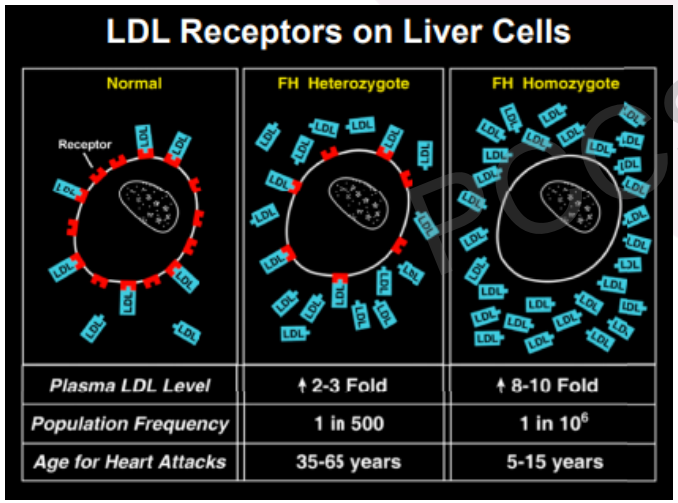
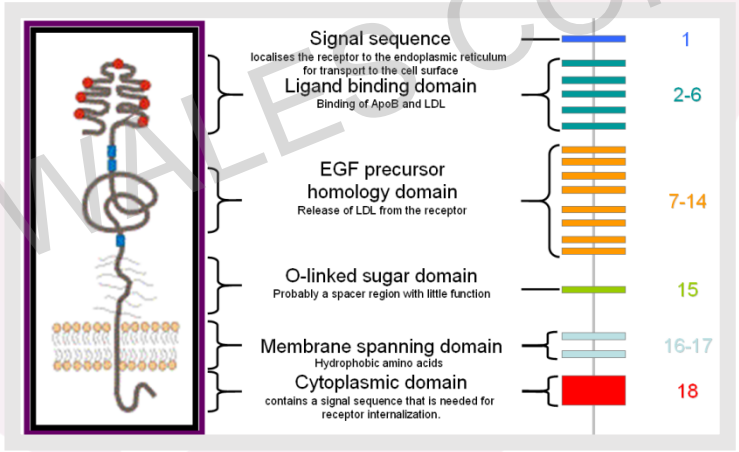
The Nobel Prize in Physiology or Medicine 1985

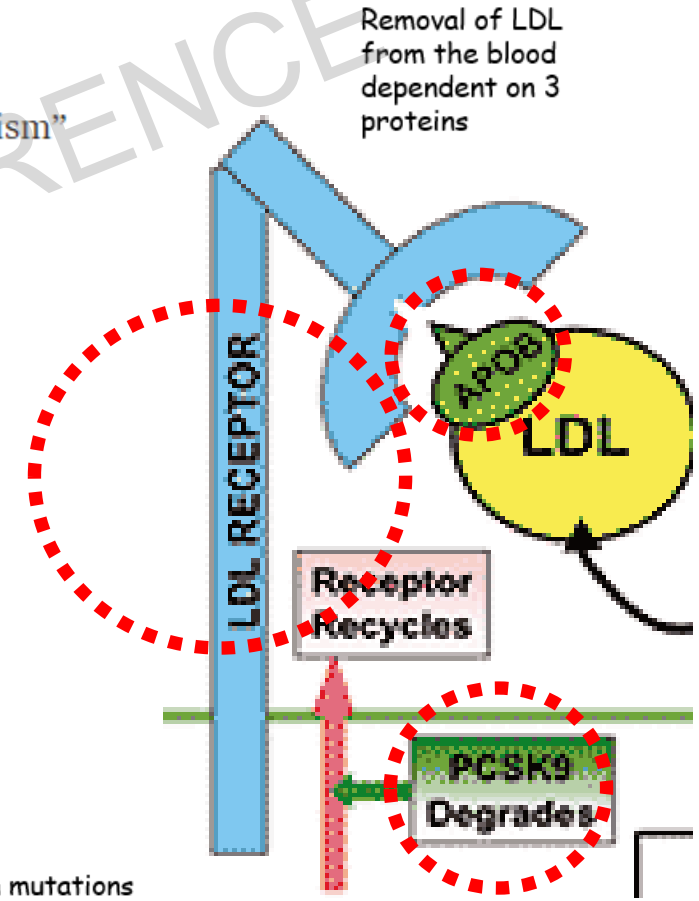
Michael S. Brown and Joseph L. Goldstein

"for their discoveries concerning the regulation of cholesterol metabolism"

Over >2000 variants known for FH







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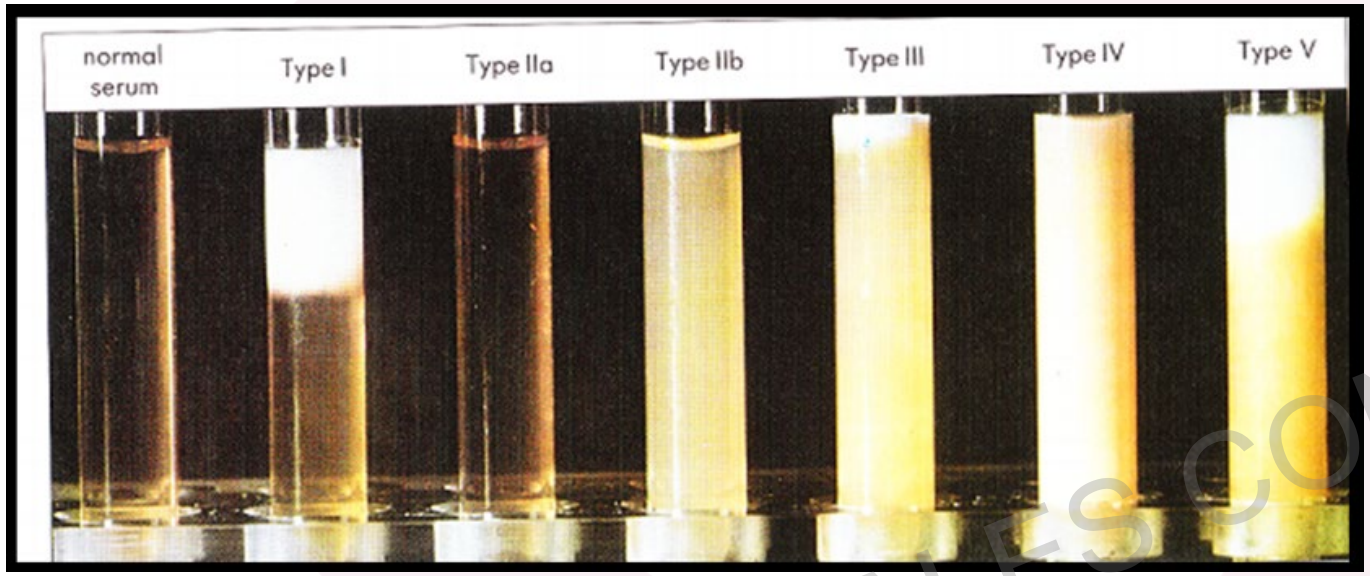
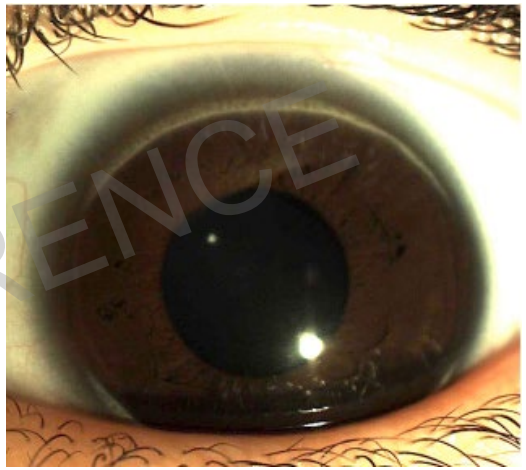
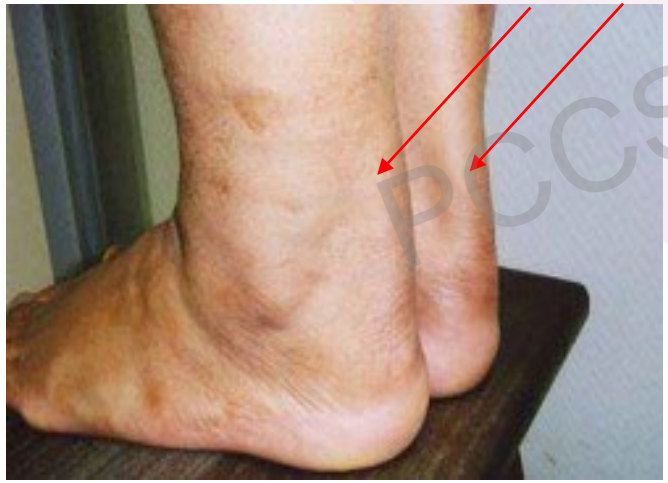
APOB, apolipoprotein B; EGF, epidermal growth factor; FH, familial hypercholesterolaemia; LDLR, low density lipoprotein receptor; PCSK9, proprotein convertase subtilisin/kexin type 9. Nair P, et al. Proceedings of the National Academy of Sciences 2013; 110:14820-14822

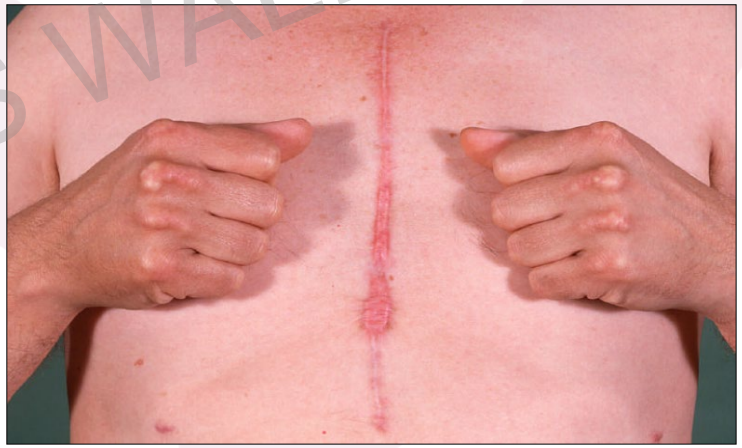
Dyslipidaemias + FH Clinical Signs

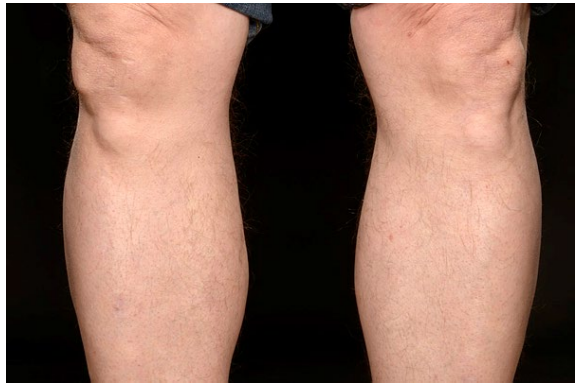




A 2.6-year-old ♂ presented with corneal arcus.
Pathogenic variants LDLR:c.1069G>A and c.2034C>A.[1]







Absence of clinical signs (for example, tendon xanthomata) in adults and children/young people does not exclude a diagnosis of FH.[2]

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FH, familial hypercholesterolaemia; LDLR, low density lipoprotein receptor. 1. Lock JH, et al. JAAPOS 2018;22:467-468; 2. NICE. Familial hypercholesterolaemia: identification and management (CG71) 2008. Available from https://www.nice.org.uk/guidance/cg71/chapter/recommendations#children-young-people. Accessed March 2022

Classification

Exclude secondary causes first:[1-3]
Hypothyroidism
Nephrotic syndrome
Cholestasis
Drugs: retinoids, cyclosporin, HAART
Poorly controlled DM
Excess alcohol

Hypercholesterolaemia

Hypertriglyceridaemia

Primary dyslipidaemia:
Predominantly hypercholesterolaemia
Predominantly hypertriglyceridaemia
Mixed dyslipidaemia

Document [redacted] 2003 (19y)

Name: [redacted]
NHS No:
DoB:
Hospital number [redacted]
Sex: F

Open Patient Record Open Test Result in Patient Record

Laboratory number: 100525241906
Requesting Site: YGCMOP Medical OP
Requestor: Not Stated (BCU)

Clinical information: borderline lipids

Result/Report origin: Blood Sciences at Ysbyty Glan Clwyd

Lipid profile (Authorised [A])

Cholesterol	10.1	mmol/L	
Triglyceride	**2.3**	**mmol/L**	**H <2.0**
HDL Cholesterol	1.3	mmol/L	>1.2
Non HDL Cholesterol	8.8	mmol/L	
Cholesterol:HDL ratio	7.8	ratio	
LDL Cholesterol	7.8	mmol/L	

Non-HDL cholesterol is reported in accordance with NICE CG 181
LDL cholesterol may not be valid for non-fasting samples.

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DM, diabetes mellitus; HAART, highly active antiretroviral therapy. 1. Ibrahim MA, et al. Hypercholesterolemia. StatPearls. Available from https://www.ncbi.nlm.nih.gov/books/NBK459188/. Accessed March 2023; 2. Heart UK. Other causes of high cholesterol. Available from https://www.heartuk.org.uk/genetic-conditions/secondary-hyperlipidaemia. Accessed March 2023; 3. NICE. Familial hypercholesterolaemia: identification and management (CG71)

Secondary Causes (Examples)

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Cause	Tests
Liver dysfunction	LFT, GGT
Hypothyroidism	TFT
Renal disease	U&E, urine dipstick
Diabetes	Fasting glucose
Drugs	thiazides, beta blockers, protease inhibitors, anti-psychotics, retinoids

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Patient A

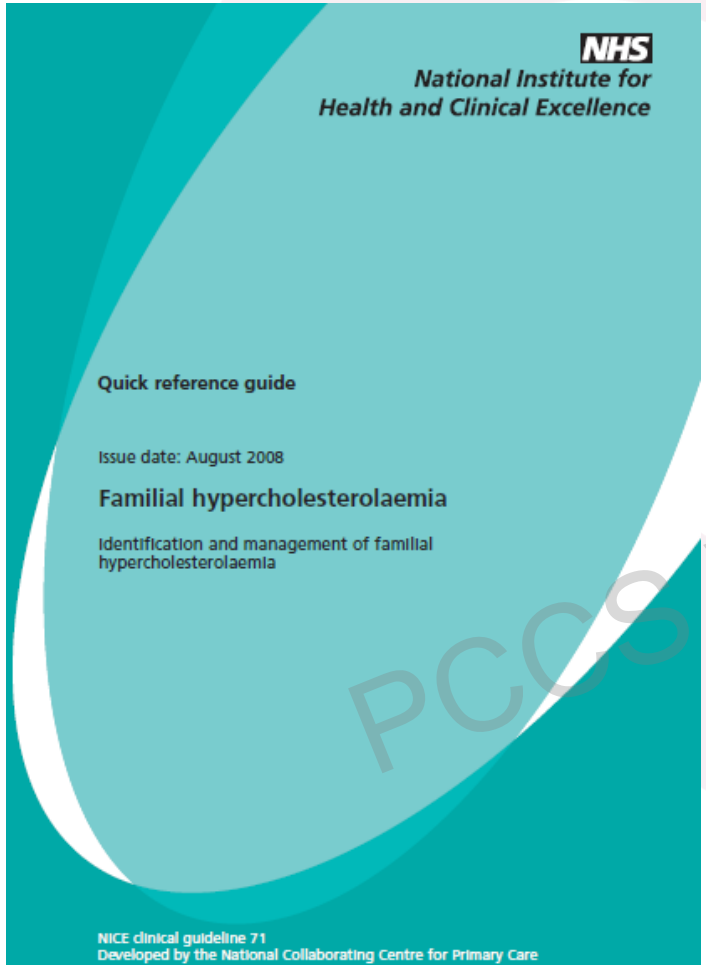
Lipid profile (AUTHORISED [A])			
Cholesterol	2.6	mmol/L	
Triglyceride	1.3	mmol/L	<2.0
HDL Cholesterol	**1.0**	**mmol/L**	**L >1.0**
Non HDL Cholesterol	1.6	mmol/L	
Cholesterol:HDL ratio	2.6	ratio	
LDL Cholesterol	1.0	mmol/L	

Patient B

Lipid profile (Authorised [A])			
Cholesterol	5.6	mmol/L	
Triglyceride	0.4	mmol/L	<2.0
HDL Cholesterol	1.8	mmol/L	>1.0
Non HDL Cholesterol	3.8	mmol/L	
Cholesterol:HDL ratio	3.1	ratio	
LDL Cholesterol	3.6	mmol/L	

GGT, gamma-glutamyltransferase; HDL, high density lipoprotein; LDL, low density lipoprotein; LFT, liver function test; TFT, thyroid function test; U&E, urea and electrolytes.

Case Finding and Diagnosis



Suspect familial hypercholesterolaemia (FH) as a possible diagnosis in adults with:

- a total cholesterol level greater than 7.5 mmol/l or a personal or family history of premature coronary heart disease (an event before 60 years in an index individual or first-degree relative). [2008, amended 2019]

Systematically search primary care records for people:

- younger than 30 years, with a total cholesterol concentration greater than 7.5 mmol/l and
- 30 years or older, with a total cholesterol concentration greater than 9.0 mmol/l as these are the people who are at highest risk of FH. [2017]

For people with a personal or family history of premature coronary heart disease (an event before 60 years in an index individual or first-degree relative), but whose total cholesterol is unknown, **offer to measure their total cholesterol. [2017]**

Carry out cascade testing using DNA testing to identify affected first- and second- and, when possible, third-degree biological relatives of people with a genetic diagnosis of FH. [2017]

PCCS WALES CONFERENCE

NICE. Familial hypercholesterolaemia: identification and management (CG71) 2008. Available from https://www.nice.org.uk/guidance/cg71/chapter/recommendations. Accessed March 2023.

Early Intervention is Best Treatment

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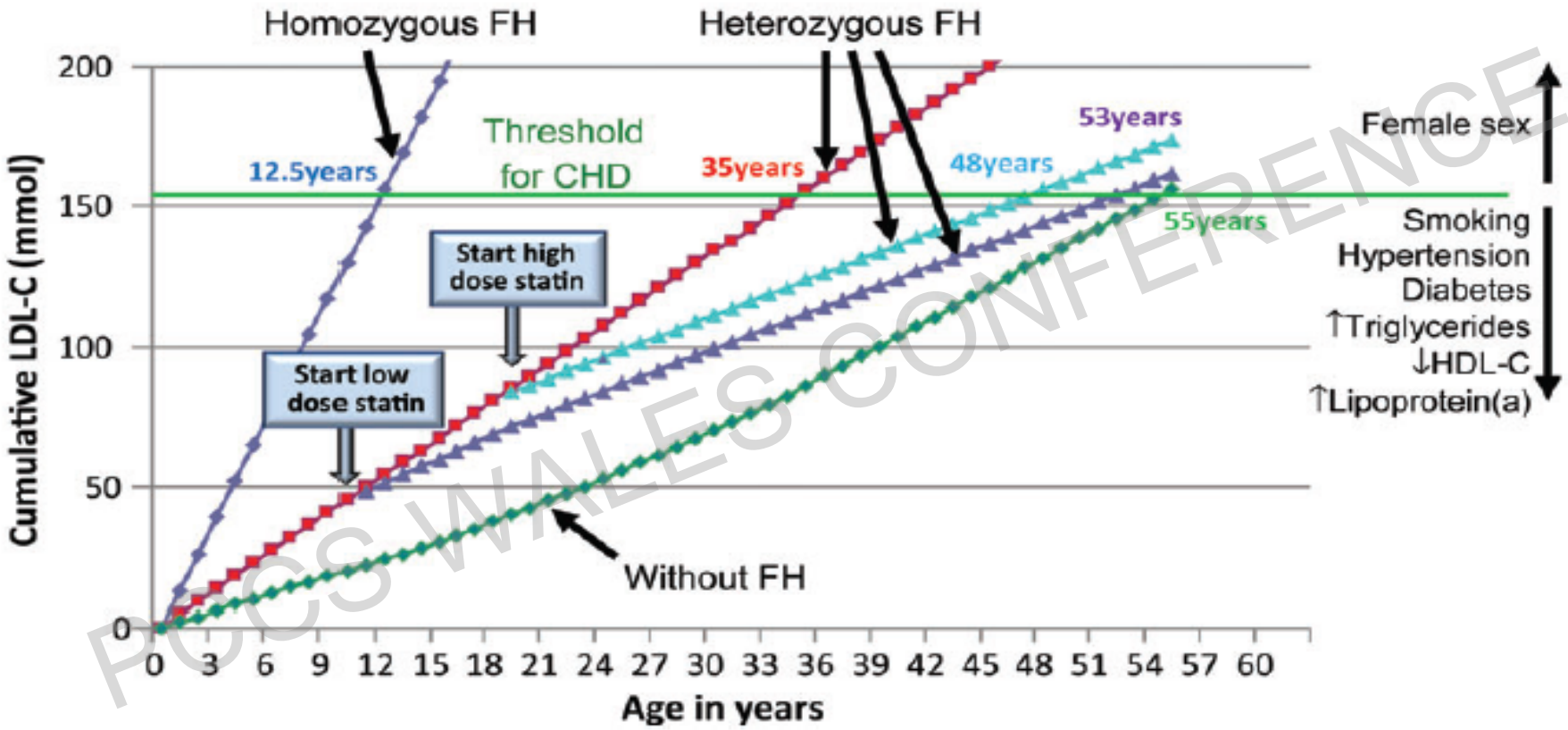

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Clinical guidelines strongly recommend early intervention with lifestyle – and statin treatment. In the young, the goal is to prevent the initial formation of atherosclerotic plaques rather than arresting or reversing growth after they have become established within the arterial wall.

CHD, coronary heart disease; FH, familial hypercholesterolaemia; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.

Prevalence of FH According to Different LDL Cholesterol Thresholds and Mutation Classification Schemes

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LDL Cholesterol Criteria	Mutation Criterion	Prevalence of FH
LDL cholesterol **≥4.9 mmol**	No mutation / variant required	1,386 of 20,485 (1 in 14)
No threshold requirement	•*LDLR* loss-of-function variant; or • *LDLR* predicted damaging rare missense variant; or • *LDLR* , *APOB* , *PCSK9* variant pathogenic in ClinVar	97 of 20,485 (1 in 211)
LDL cholesterol **≥4.9 mmol**	•*LDLR* loss-of-function variant; or •any rare *LDLR* missense variant	80 of 20,485 (1 in 256)
LDL cholesterol **≥3.36 mmol**	•*LDLR* loss-of-function variant: or • *LDLR* predicted damaging rare, missense variant; or • *LDLR* , *APOB* , *PCSK9* variant pathogenic in ClinVar	68 of 20,485 (1 in 301)
No threshold requirement	•*LDLR* loss-of-function variant; or • *LDLR* predicted damaging rare missense variant	60 of 20,485 (1 in 341)
LDL cholesterol **≥4.9 mmol**	•*LDLR* loss-of-function variant; or • *LDLR* predicted damaging rare missense variant; or • *LDLR, APOB* , *PCSK9* variant pathogenic in ClinVar	24 of 20,485 (1 in 853)

Note: A substantial proportion of individuals with high LDL-C have 'Polygenic' causes (involving several loci throughout the genome).

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APOB, apolipoprotein B; FH, familial hypercholesterolaemia; LDL-C, low density lipoprotein cholesterol; LDLR, low density lipoprotein receptor; PCSK9, proprotein convertase subtilisin/kexin type 9.

Impact of FH Mutation Status on CAD According to LDL-C

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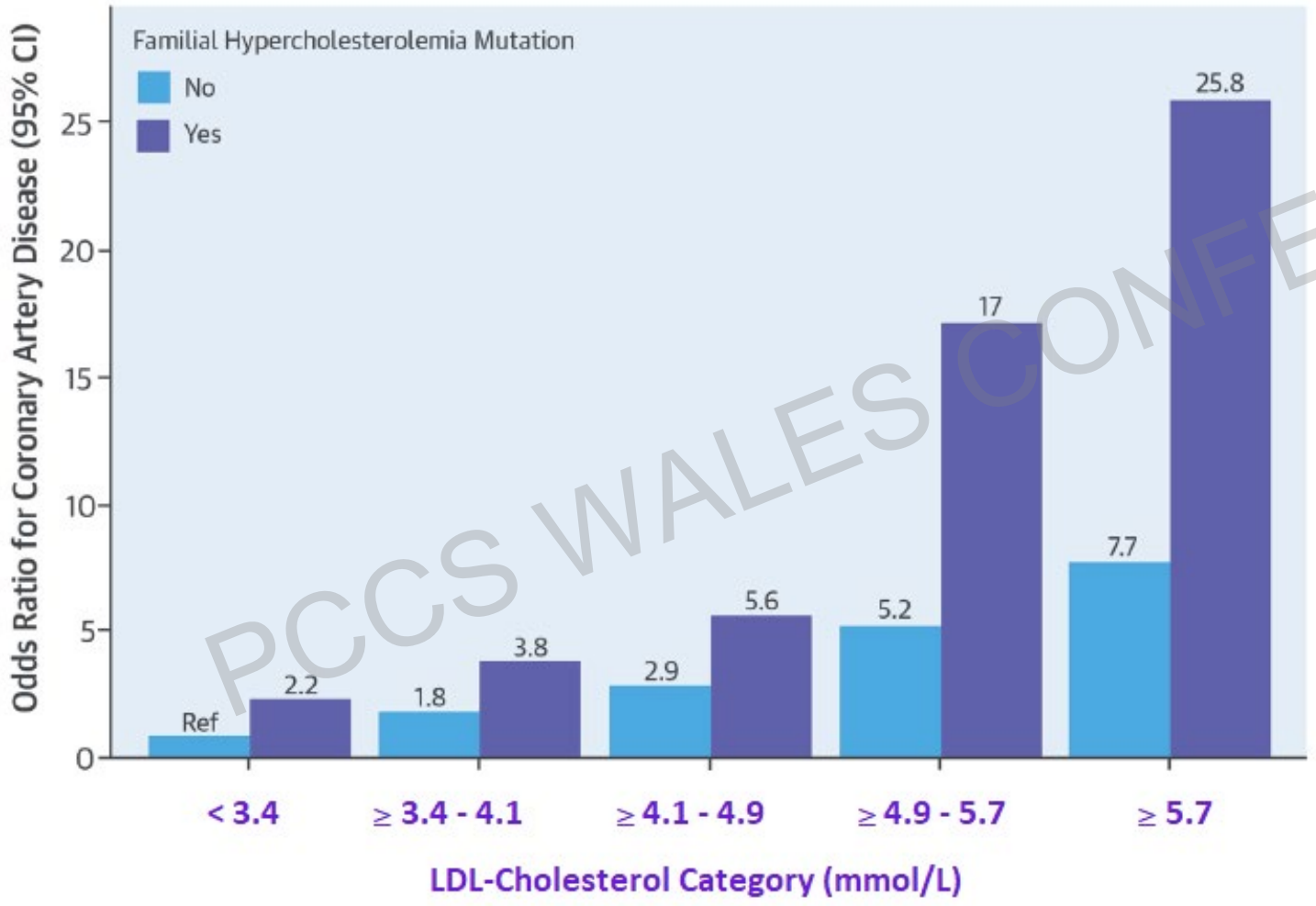

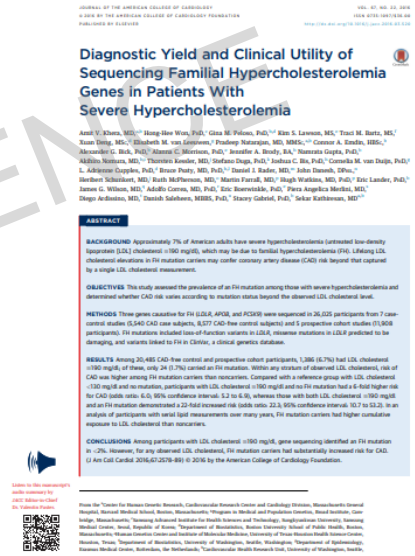

Diagnostic Yield and Clinical Utility of Sequencing Familial Hypercholesterolemia Genes in Patients With Severe Hypercholesterolemia

ABSTRACT

BACKGROUND Approximately 7% of American adults have severe hypercholesterolemia (untreated low-density lipoprotein [LDL] cholesterol ≥190 mg/dl), which may be due to familial hypercholesterolemia (FH). Lifelong LDL cholesterol elevations in FH mutation carriers may confer coronary artery disease (CAD) risk beyond that captured by a single LDL cholesterol measurement.

OBJECTIVES This study assessed the prevalence of an FH mutation among those with severe hypercholesterolemia and determined whether CAD risk varies according to mutation status beyond the observed LDL cholesterol level.

METHODS Three genes causative for FH (*LDLR*, *APOB*, and *PCSK9*) were sequenced in 26,025 participants from 7 case-control studies (5,540 CAD case subjects, 8,577 CAD-free control subjects) and 5 prospective cohort studies (71,908 participants). FH mutations included loss-of-function variants in *LDLR*, missense mutations in *LDLR* predicted to be damaging, and variants linked to FH in ClinVar, a clinical genetics database.

RESULTS Among 20,485 CAD-free control and prospective cohort participants, 1,386 (6.7%) had LDL cholesterol ≥190 mg/dl; of these, only 24 (1.7%) carried an FH mutation. Within any stratum of observed LDL cholesterol, risk of CAD was higher among FH mutation carriers than noncarriers. Compared with a reference group with LDL cholesterol <130 mg/dl and no mutation, participants with LDL cholesterol ≥190 mg/dl and no FH mutation had a 6-fold higher risk for CAD (odds ratio: 6.0; 95% confidence interval: 5.2 to 6.9), whereas those with both LDL cholesterol ≥190 mg/dl and an FH mutation demonstrated a 22-fold increased risk (odds ratio: 22.1; 95% confidence interval: 10.7 to 53.2). In an analysis of participants with serial lipid measurements over many years, FH mutation carriers had higher cumulative exposure to LDL cholesterol than noncarriers.

CONCLUSIONS Among participants with LDL cholesterol ≥190 mg/dl, gene sequencing identified an FH mutation in ~2%. However, for any observed LDL cholesterol, FH mutation carriers had substantially increased risk for CAD.

(J Am Coll Cardiol 2016;67:2578-89) © 2016 by the American College of Cardiology Foundation.

Conclusions: **For any observed LDL cholesterol, FH mutation carriers had substantially increased risk for CAD.**

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CAD, coronary artery disease; CI, confidence interval; FH, familial hypercholesterolaemia; LDL-C, low density lipoprotein cholesterol.
Khera AV, et al. J Am Coll Cardiol 2016;67:2578-2589

FH Genotype Reports + SNP Scores

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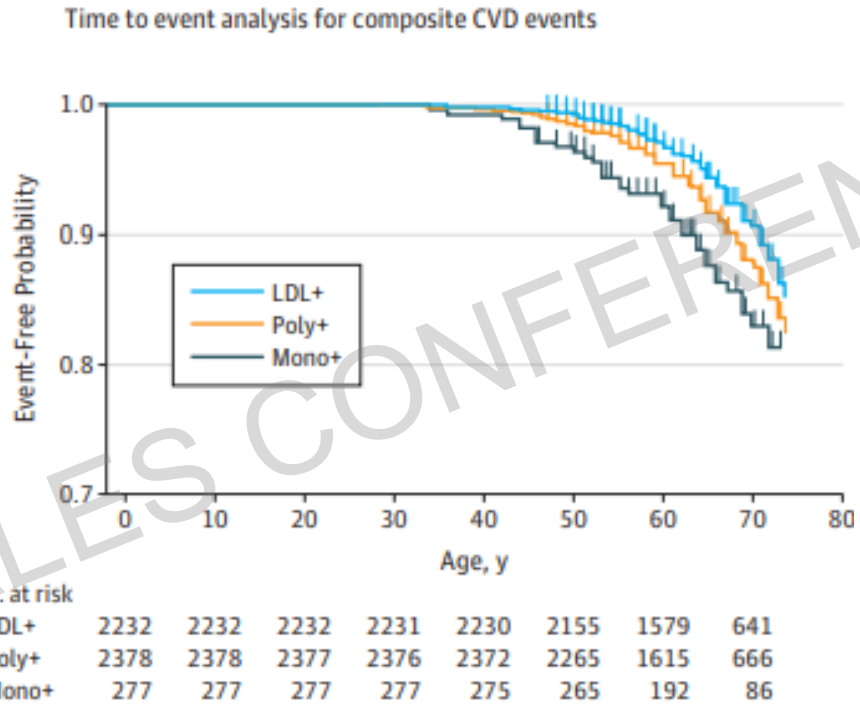
Association of Monogenic vs. Polygenic Hypercholesterolemia With Risk of Atherosclerotic Cardiovascular Disease

	LDL-C weighted score in WHII controls		Measured LDL-C (mmol/L) in WHII controls, mean (SD)	WHII controls with LDL-C >4·9 mmol/L		Risk ratio (95% CI) of LDL-C >4·9 mmol/L*
	Mean (SD)	Range		Measured	Predicted	
Decile 1	0·43 (0·14)	−0·5 to 0·58	3·76 (0·95)	36/299 (12%)	51/302 (17%)	NA
Decile 2	0·66 (0·04)	0·58 to 0·73	3·99 (0·88)	43/296 (15%)	69/302 (23%)	1·21 (0·80–1·82)
Decile 3	0·77 (0·03)	0·73 to 0·81	4·21 (0·96)	71/300 (24%)	82/302 (27%)	1·97 (1·36–2·84)
Decile 4	0·85 (0·02)	0·81 to 0·88	4·34 (0·95)	85/298 (29%)	88/303 (29%)	2·37 (1·66–3·38)
Decile 5	0·91 (0·02)	0·88 to 0·93	4·36 (0·94)	80/300 (27%)	94/302 (31%)	2·21 (1·55–3·17)
Decile 6	0·96 (0·01)	0·94 to 0·98	4·48 (0·91)	96/298 (32%)	100/302 (33%)	2·68 (1·89–3·79)
Decile 7	1·00 (0·01)	0·98 to 1·02	4·50 (1·00)	102/295 (35%)	106/302 (35%)	2·87 (2·04–4·05)
Decile 8	1·05 (0·02)	1·02 to 1·08	4·56 (0·93)	96/292 (33%)	108/301 (36%)	2·73 (1·93–3·87)
Decile 9	1·12 (0·02)	1·08 to 1·16	4·68 (1·05)	120/294 (41%)	118/302 (39%)	3·39 (2·42–4·74)
Decile 10	1·23 (0·06)	1·16 to 1·46	4·90 (0·99)	148/295 (50%)	130/302 (43%)	4·17 (3·01–5·78)

Please see appendix for details of how we predicted the LDL-C values. LDL-C=low-density lipoprotein cholesterol. WHII=Whitehall II. NA=not applicable. *Decile 1 used as reference.

Table 3: Outcome data in Whitehall II controls according to weighted LDL-C gene score deciles



Conclusion:
Genetic determinants of LDL-C levels impose additional risk of CVD

Clinical Summary: Family history of premature CHD.
Baseline 2001: Cholesterol 9.1, LDL 6.8, Trig 0.9. For FH NGS analysis.

Familial Hypercholesterolaemia Results

Sequence Analysis	*LDLR* Dosage Analysis	LDL-c raising SNP score
No Pathogenic Variant Detected	No Duplications or Deletions Detected	Score: 1.213 Decile: 10
Report Summary	FH not confirmed High Likelihood of Polygenic Hypercholesterolaemia	
SLCO1B1 polymorphisms[1,2]:	rs2306283 genotype A/G	rs4149056 genotype T/T

Please refer to the suggested references below for further guidance

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CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; FH, familial hypercholesterolaemia; LDL-C, low density lipoprotein cholesterol; LDLR, low density lipoprotein receptor; SD, standard deviation; SNP, single nucleotide polymorphisms. 1. Trinder M, et al. JAMA Cardiol 2020; 5:390-399; 2. Talmud PJ, et al. Lancet 2013; 381:1293-1301

Case Finding??

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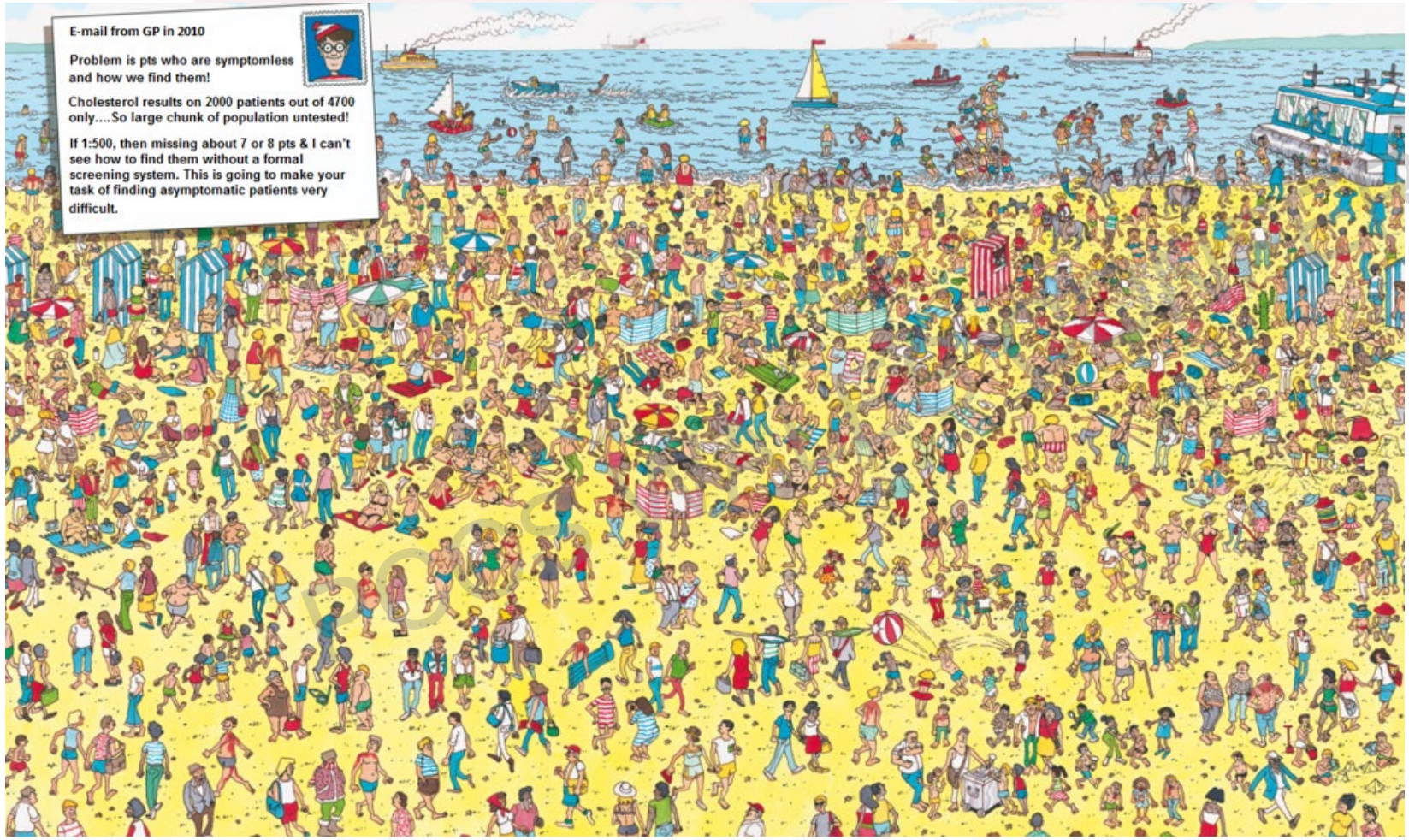
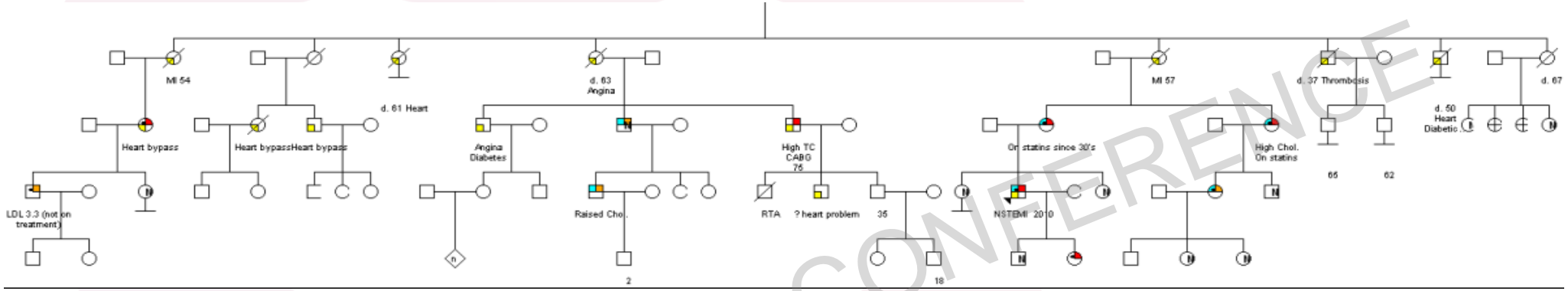


Case History – One Family's Experience of FH...



41 year old fit and active civil servant:

- Admitted on Boxing Day 2010 with central chest pain
- Anterior NSTEMI, Tchol 9.7 mmol/L
- Transferred to Liverpool Heart & Chest Hosp:
  - proximal LAD 99% stenosis (PCI to LAD)
  - Good recovery post PCI

Currently 20 individuals have been tested within family
8 people tested +ve (offered treatment), 12 tested –ve

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FH, familial hypercholesterolaemia; LAD, left anterior descending artery; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; Tchol, total cholesterol. British Heart Foundation. Life with Familial Hypercholesterolaemia. Available from https://www.bhf.org.uk/informationsupport/publications/heart-conditions/m111f-inherited-heart-conditions---familial-hypercholesterolaemia. Accessed March 2023

FH Case-Finding: FAMCAT

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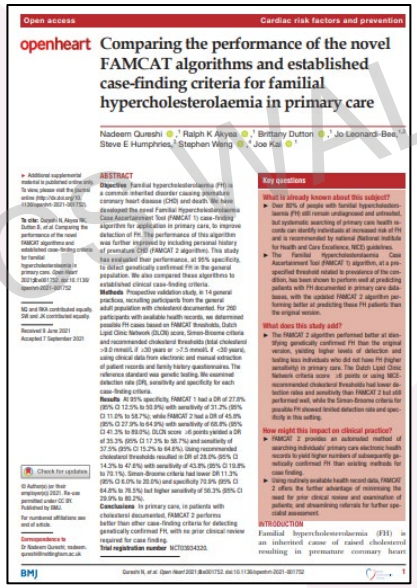
Open access Cardiac risk factors and prevention

openheart

Comparing the performance of the novel FAMCAT algorithms and established case-finding criteria for familial hypercholesterolaemia in primary care

Nadeem Qureshi [1], Ralph K Akyea [1], Brittany Dutton [1], Jo Leonardi-Bee [1,2], Steve E Humphries [3], Stephen Weng [4], Joe Kai [1]

Open Heart: first published as 10.1136/openhrt-2021-



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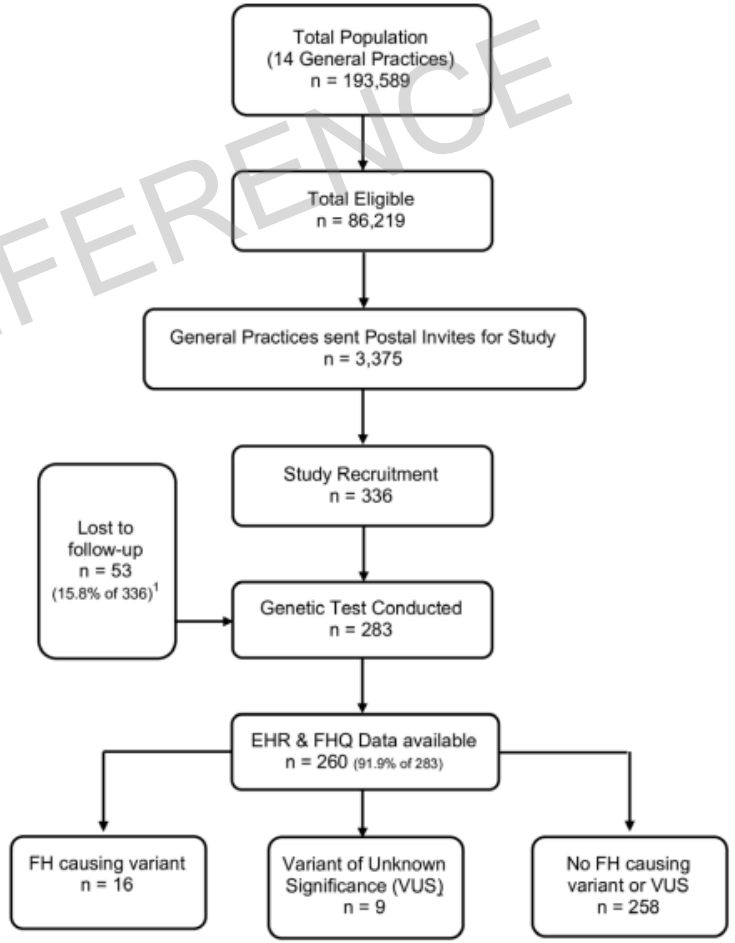

PCCS WALES CONFERENCE

EHR, electronic health record; FAMCAT, Familial Hypercholesterolaemia Case Ascertainment Tool; FH, familial hypercholesterolaemia; FHQ, family history questionnaire.
Qureshi N, et al. Open Heart 2021;8:e001752

BCUHB Cholesterol Tests (12m) (n=170910; assume >600 FH)

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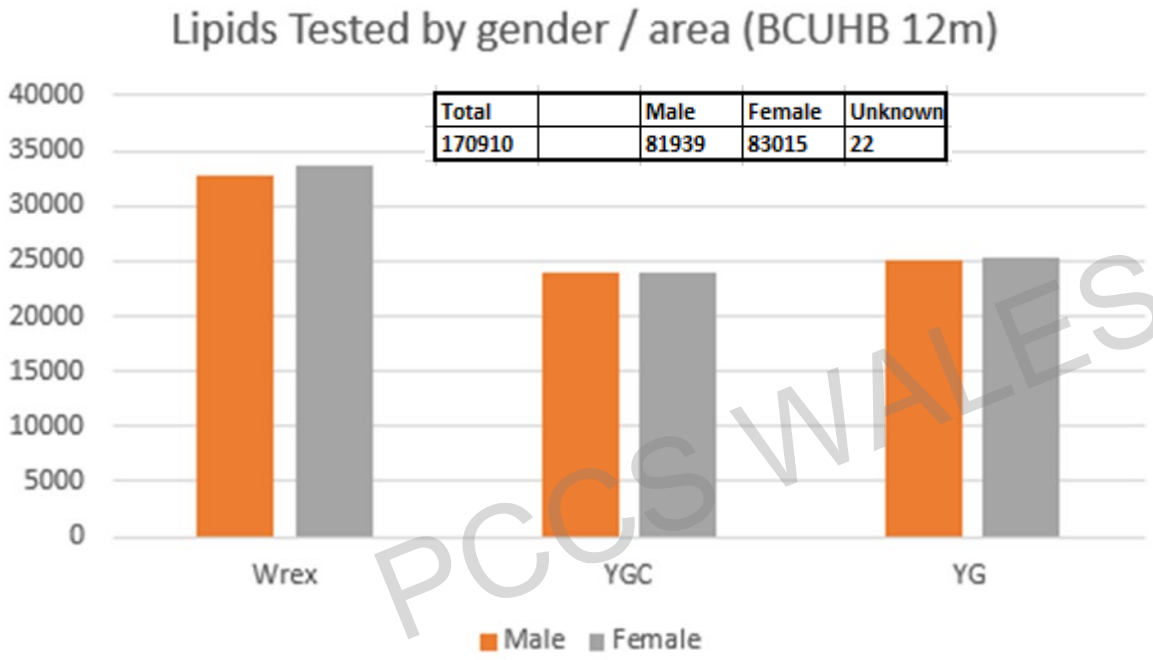

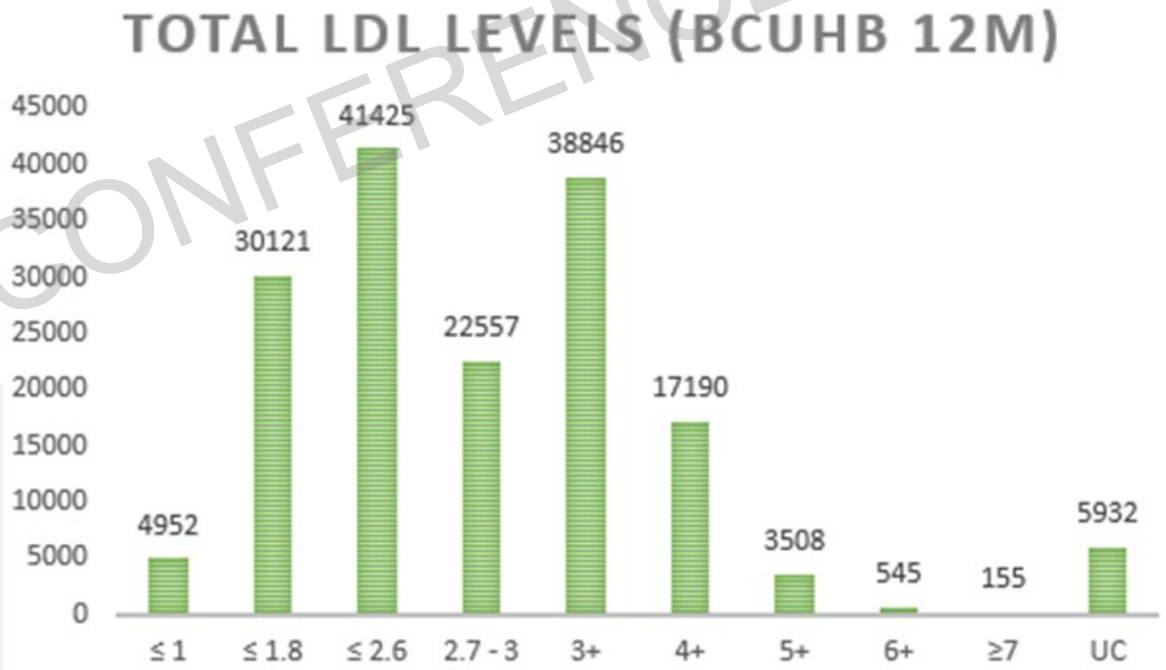

BCUHB, Betsi Cadwaladr University Health Board; FH, familial hypercholesterolaemia; LDL, low density lipoprotein; Wrex, Wrexham; YG, Ysbyty Gwynedd; YGC, Ysbyty Glan Clwyd.
Speaker's own practice

(BCUHB) LDL Data / Daily Lists

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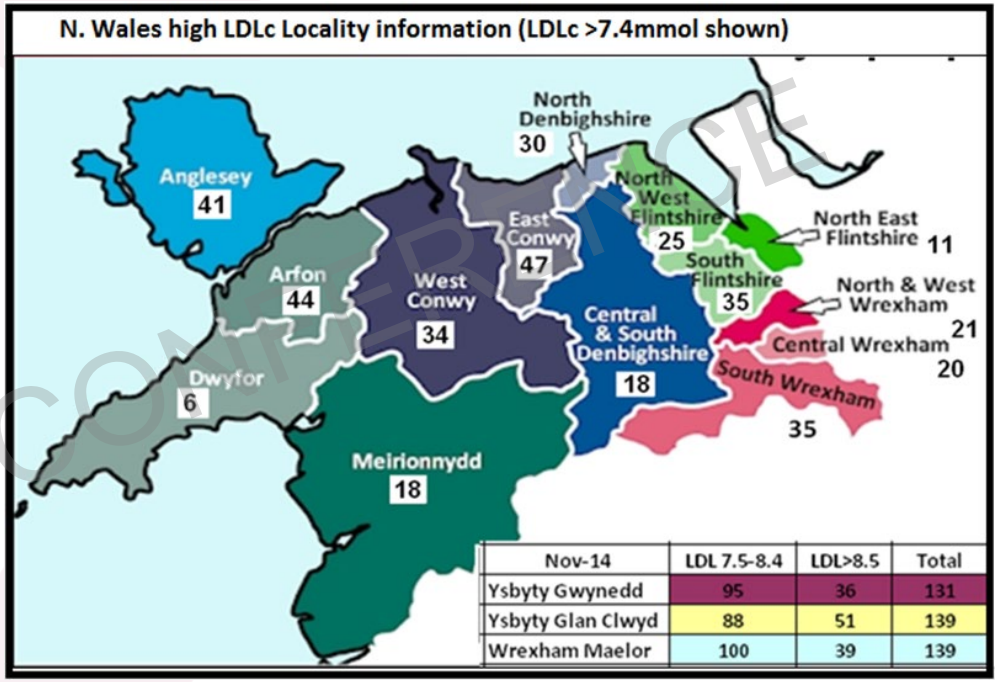
1E+09	[redacted]	######	######	51	[redacted]	H	F	######	######	5.2
1E+09		######	######	69			F	######	######	5.1
1E+09		######	######	47			M	######	######	5.8
1E+09		######	######	37			F	######	######	5.2
1E+09		######	######	67			M	######	######	5.3
1E+09		######	######	66			M	######	######	5.1
1E+09		######	######	60		H	F	######	######	6.2
1E+09		######	######	66			M	######	######	5.3
7E+09		######	######	37			F	######	######	6.8
7E+09		######	######	66			F	######	######	5.1
7E+09		######	######	76			F	######	######	5
7E+09		######	######	23		T	F	######	######	10.4
7E+09		######	######	74		N	M	######	######	5
7E+09		######	######	52			F	######	######	6.6
1E+09		######	######	72		J	F	######	######	5
1E+09		######	######	57			F	######	######	6.4
1E+09		######	######	58			F	######	######	7.5
1E+09		######	######	56			F	######	######	6.4
1E+09		######	######	82			F	######	######	5.6
1E+09		######	######	63			F	######	######	5.6
1E+09		######	######	61			M	######	######	5.5
1E+09		######	######	85			F	######	######	5
7E+09		######	######	51			M	######	######	5.6
7E+09		######	######	61			F	######	######	5.2
7E+09		######	######	64			M	######	######	5.7
7E+09		######	######	52			F	######	######	5.4
7E+09		######	######	77			F	######	######	5.1
7E+09		######	######	45			M	######	######	5
7E+09		######	######	70			F	######	######	5.8
7E+09		######	######	82			F	######	######	5.4



Nov-14	LDL 7.5-8.4	LDL>8.5	Total
Ysbyty Gwynedd	95	36	131
Ysbyty Glan Clwyd	88	51	139
Wrexham Maelor	100	39	139

	Jan	Feb	March	Apr	May	June	July	Aug	Sept	Oct	Nov	Dec	Total	Ave week
2019	0	0	0	0	0	0	0	0	0	376	379	199	954	73
2020	382	325	223	45	70	145	251	196	258	280	275?	118	2293	44
2021	277	210	344	360	301	187	266	277	245	216	296	223	3202	62
2022	411	460	517	436	474	432	432	400	407	251	289	211	4720	91
2023	358	318	0	0	0	0	0	0	0	0	0	0	676	

	>8.5	7.5 - 8.4	6.5 - 7.4
W91005	5	9	19
W91029	5	2	13
W91032	2	0	7
W91037	0	1	9
W91046	3	3	12
W91055	0	4	14
W91636	0	2	9
39,080	15	21	83

PCOS WALES CONFERENCE

BCUHB, Betsi Cadwaladr University Health Board; LDL, low density lipoprotein.
Speaker's own practice

High LDLc Alerts – Inpatient / Cardiology (Cath lab setting)

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Prior to Alerts, in 2015 – 2072 patients attended N. Wales Cardiac Centre / Cath lab; **29** (1.4% had history of LDLc ≥6,5mmol)
Collectively, these pts + those attending for Echo, Pacing +/- ICD in Ysbyty Glan Clwyd n=8625. ~0.6% on high LDL list

N. Wales Cardiology (2015) High LDL pt attendances

Cardiology Activity (not routine outpatient appointments)				
LDLC mmol	6.5-7.4	7.5-8.4	>8.5	Total
Number	46	8	3	57
Number seen	16	5	0	21
Percent	35%	63%	0%	37%

~2/3rds not seen

Missed Opportunity !!

Following initiating automated Alerts – **All Alert cardiology in-patients routinely seen +/- offered genotyping for FH** (~1% of Catheter Lab pts)

Patient contact notification service
BCU PATIENT CONTACT ALERT
To Robert Gingell (BCUHB - Acute Medicine)

Chemical Pathology Y.G.C
Patient Enquiry. Cumulative results

Reg	S E T [LIPH]	Surname	Inits		
[redacted]		[redacted]	[redacted]		
021203	* 8.9	1.9	1.05	7.0	

High LDL alert

Patient identifier: [redacted] (NHS Number)
Patient name: [redacted]
Contact type: Ward admission
Ward: Cardiac Catheter Laboratory
Site: Glan Clwyd Hospital

Alert allows All (historic) high LDLc Cardiac Pts to be offered Genotyping

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BCUHB, Betsi Cadwaladr University Health Board; ICD, implantable cardioverter defibrillator; FH, familial hypercholesterolaemia; LDLc, low density lipoprotein cholesterol; YGC, Ysbyty Glan Clwyd.
Speaker's own practice

Cath Lab FH Patient Case

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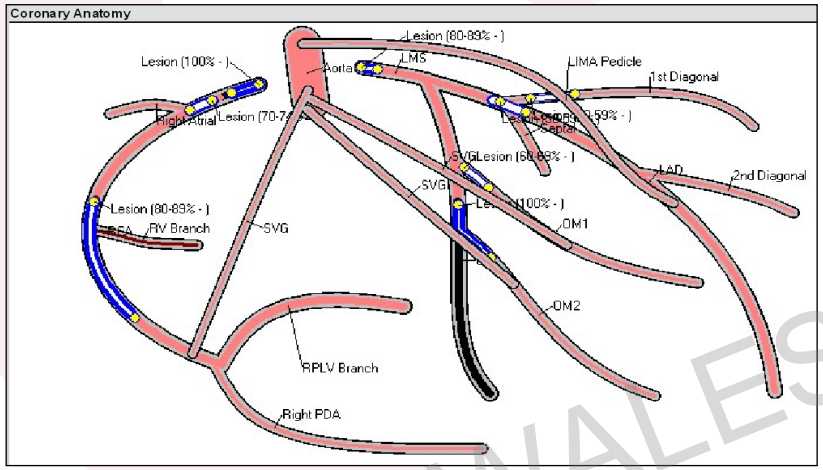
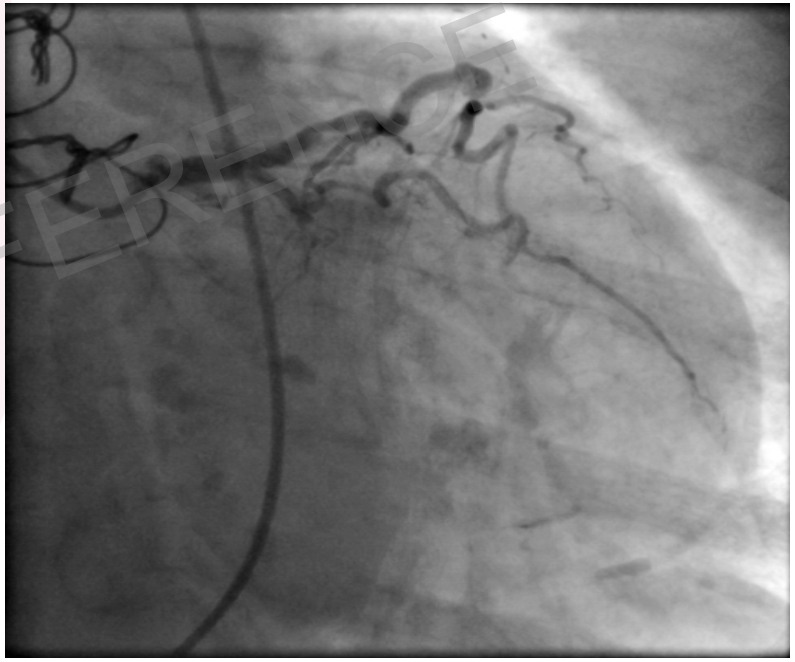
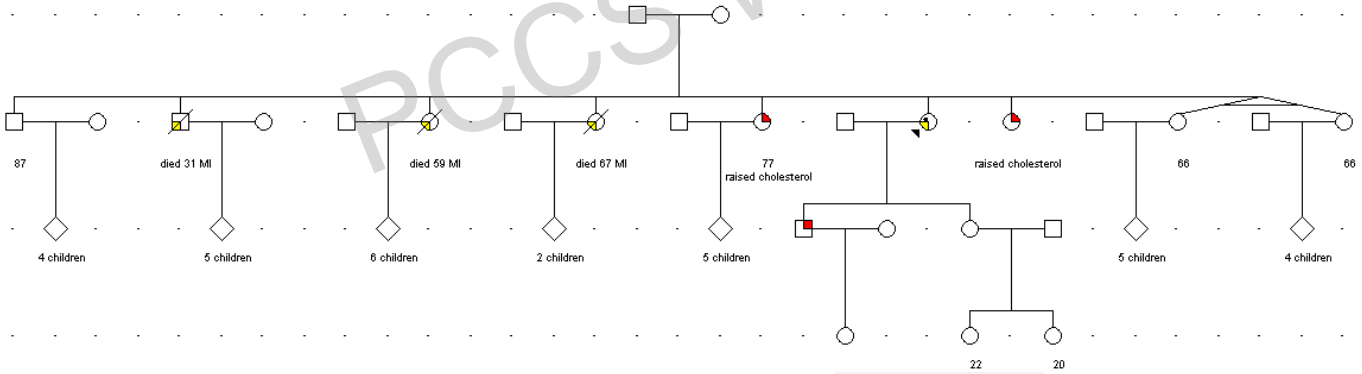
74 year old lady (LDL>8.5mmol) +ve FH







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FH, familial hypercholesterolaemia; LDL, low density lipoprotein.
Speaker's own practice

All Wales FH Service

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Genetic Interest Group | H·E·A·R·T UK THE CHOLESTEROL CHARITY | Health Challenge Wales | Her Iechyd Cymru

Grŵp Cydlynu Rhwydwaith y Galon
Cardiac Networks Co-ordinating Group

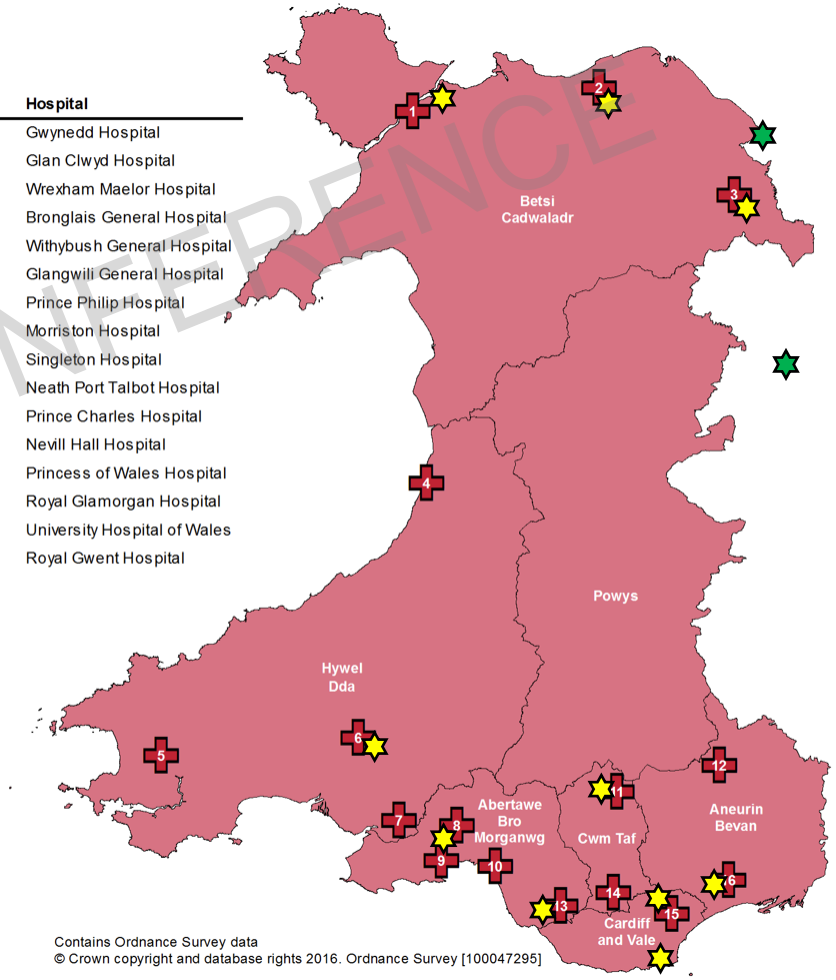
A British Heart Foundation Heart Support Group

WALES FAMILIAL HYPERCHOLESTEROLAEMIA CASCADE SCREEENING PROGRAMME

LAUNCH INVITATION **9th December 2010**

Edwina Hart - Minister for Health and Social Services

Key	Hospital
1	Gwynedd Hospital
2	Glan Clwyd Hospital
3	Wrexham Maelor Hospital
4	Bronglais General Hospital
5	Withybush General Hospital
6	Glangwili General Hospital
7	Prince Philip Hospital
8	Morriston Hospital
9	Singleton Hospital
10	Neath Port Talbot Hospital
11	Prince Charles Hospital
12	Nevill Hall Hospital
13	Princess of Wales Hospital
14	Royal Glamorgan Hospital
15	University Hospital of Wales
16	Royal Gwent Hospital



Contains Ordnance Survey data
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FH, familial hypercholesterolaemia.
Map adapted from: Welsh Parliament. Redesigning hospital services. Available from https://research.senedd.wales/research-articles/redesigning-hospital-services/. Accessed April 2023

CROSS BORDER Issues

Eligibility for Familial Hypercholesterolaemia genotyping:

	1	2	3	4
Patient resident in	England	England	Wales	Wales
Registered GP surgery in	England	Wales	England	Wales
Eligible for All Wales FH Genotyping	No	Yes	Yes	Yes

FREE PRESCRIPTIONS[1,2]

As of 1 April 2007, prescription charges were abolished for Welsh patients in Wales, including all patients registered with a Welsh GP who fill their prescriptions from Welsh pharmacists and those patients with an English GP as long as they fill their prescription from a Welsh pharmacist and present their entitlement card.

FH, familial hypercholesterolaemia; GP, general practitioner. 1. Llywodraeth Cymru Welsh Government. Free prescriptions are a long term investment in people's health – Vaughan Gething. April 2017. Available from https://www.gov.wales/free-prescriptions-are-long-term-investment-peoples-health-vaughan-gething-0#:~:text=Since%201%20April%202007%20prescription,experts%20able%20to%20prescribe%20medication. Accessed March

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Top 20 Commonest Variants Found in Wales

Mutation (1)	North	Powys	South East	South West	Grand Total
APOB:c.10580G>A	54	2	72	51	179
LDLR:c.1816G>T	52	1	31	23	107
Deletion of exon 7	52		7	29	88
LDLR:c.301G>A	41		30	5	76
LDLR:c.2042G>C	1		9	40	50
LDLR:c.1444G>A	17	1	11	19	48
LDLR:c.313+1G>A	16		13	12	41
LDLR:c.2054C>T	24		9	6	39
LDLR:c.118del			32	1	33
LDLR:c.1217G>C			31		31
LDLR:c.1745T>C	3		19	8	30
LDLR:c.1285G>A	2	3	19	5	29
LDLR:c.1061A>T			12	13	25
LDLR:c.1133A>C	1		19	5	25
LDLR:c.1436T>C	3		8	9	20
LDLR:c.1897C>T	5		12	3	20
LDLR:c.1048C>T	8		5	5	18
LDLR:c.1447T>C	8	3	7		18
APOE:c.500_502del	2		13	2	17
LDLR:c.136T>G	2		1	14	17

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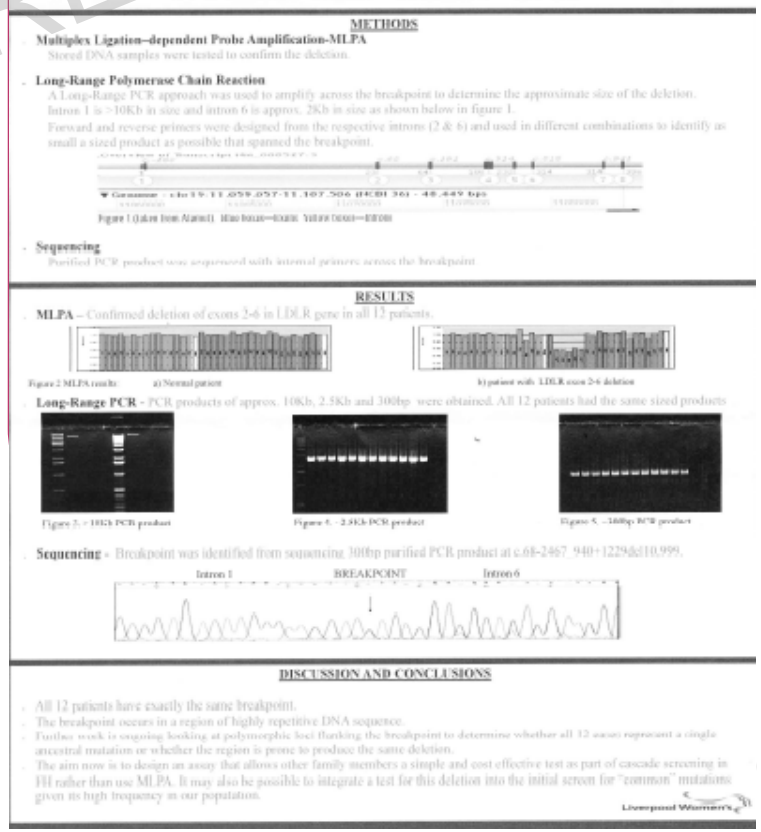
Characterisation of the deletion breakpoints in Familial Hypercholesterolemia families with a common deletion of exons 2-6 of the LDLR gene

Frances White[1], Julie Sibbring[1], Alison Taylor[1], Janice Harland[1] and Roger Mountford[1]

common deletion of exons 2-6 of the LDLR gene

This deletion is the most common mutation in the LDLR gene detected to date in the North-West Region of the UK.



METHODS

Multiplex Ligation–dependent Probe Amplification-MLPA

Long-Range Polymerase Chain Reaction

Sequencing

RESULTS

MLPA – Confirmed deletion of exons 2-6 in LDLR gene in all 12 patients.

Long-Range PCR - PCR products of approx. 10Kb, 2.5Kb and 300bp were obtained. All 12 patients had the same sized products

Sequencing - Breakpoint was identified from sequencing 300bp purified PCR product at c.68-2467_940+1229del10,999.

Intron 1 BREAKPOINT Intron 6

DISCUSSION AND CONCLUSIONS

All 12 patients have exactly the same breakpoint.

The breakpoint occurs in a region of highly repetitive DNA sequence.

Liverpool Women's

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ApoB, apolipoprotein B; ApoE, apolipoprotein E; LDLR, low density lipoprotein receptor; PCSK9, proprotein convertase subtilisin/kexin type 9; UK, United Kingdom.

All Wales FH Service Genotyping Figures (Jan 2023)

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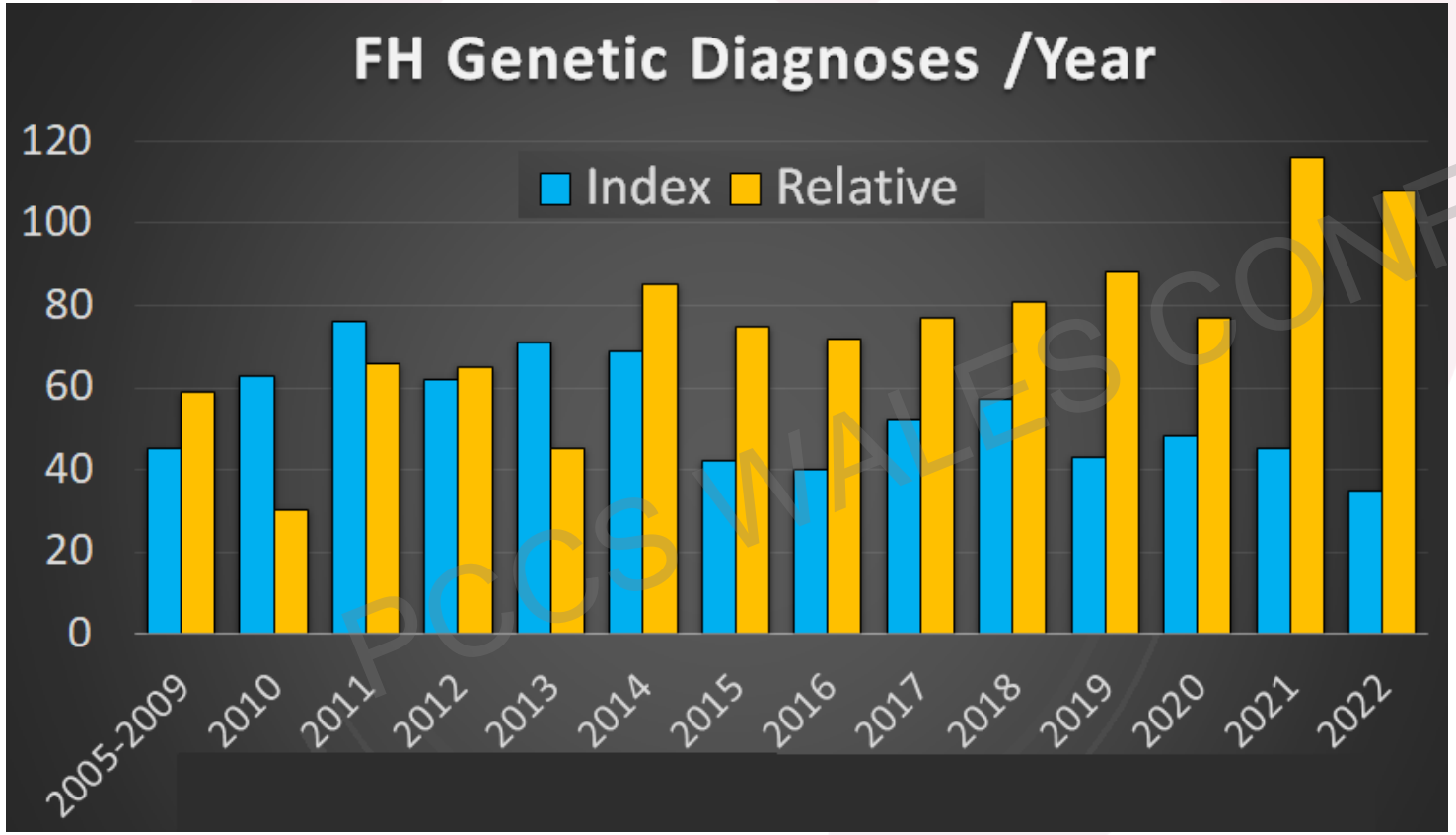

~2.6 Relatives Tested per Index (Range 0 – 31)

5453 patients genotyped

3499 indexes

1954 relatives

748 +ve

1051 +ve

903 -ve

1799 +ve

~15% of FH pts identified

85 of 748

LDLR Mild mutations/ reduced penetrance

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FH, familial hypercholesterolaemia; LDLR, low density lipoprotein receptor; pts, patients.
Speaker's own practice

Mild Pathogenic / Reduced Penetrance Mutations Identified in Wales So Far..

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- *APOB*
  - APOB:c.10580G>A - 89 index patients (most common mutation, 12%)
- Mild *LDLR* mutations
  - 85 indexes with known mild *LDLR* mutations
  - LDLRc.1816G>T - 39 index patients (2nd most common mutation, 5%)
- Challenges of cascade testing of mild mutations

ApoB, apolipoprotein B; LDLR, low density lipoprotein receptor.
All Wales FH Genotype data Jan 2023 - Thanks to Kate Haralambos Network Manager

Drugs – prescribing category

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Drugs	BRAG (Formulary Status)
All statins	Green (GP first choice)
Ezetimibe	Green (GP prescribe – 2nd line)
Fibrates	Green
Colesevelam	Amber
Bempedoic Acid	Amber
Alirocumab & Evolocumab	Red
Inclisiran	Red
Omacor (Omega-3-Acid Ethyl Esters)	Amber
Icosapent ethyl	Blue (awaiting NICE)

Green – Primary care and secondary care prescribing
Amber – Secondary care initiation, primary care continuation
Red – Secondary care prescribing only

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BRAG, blue, red, amber, green; GP, general practitioner; NICE, National Institute for Health and Care Excellence.

Case: PCSK9 GoF & Premature IHD 31yo ♂

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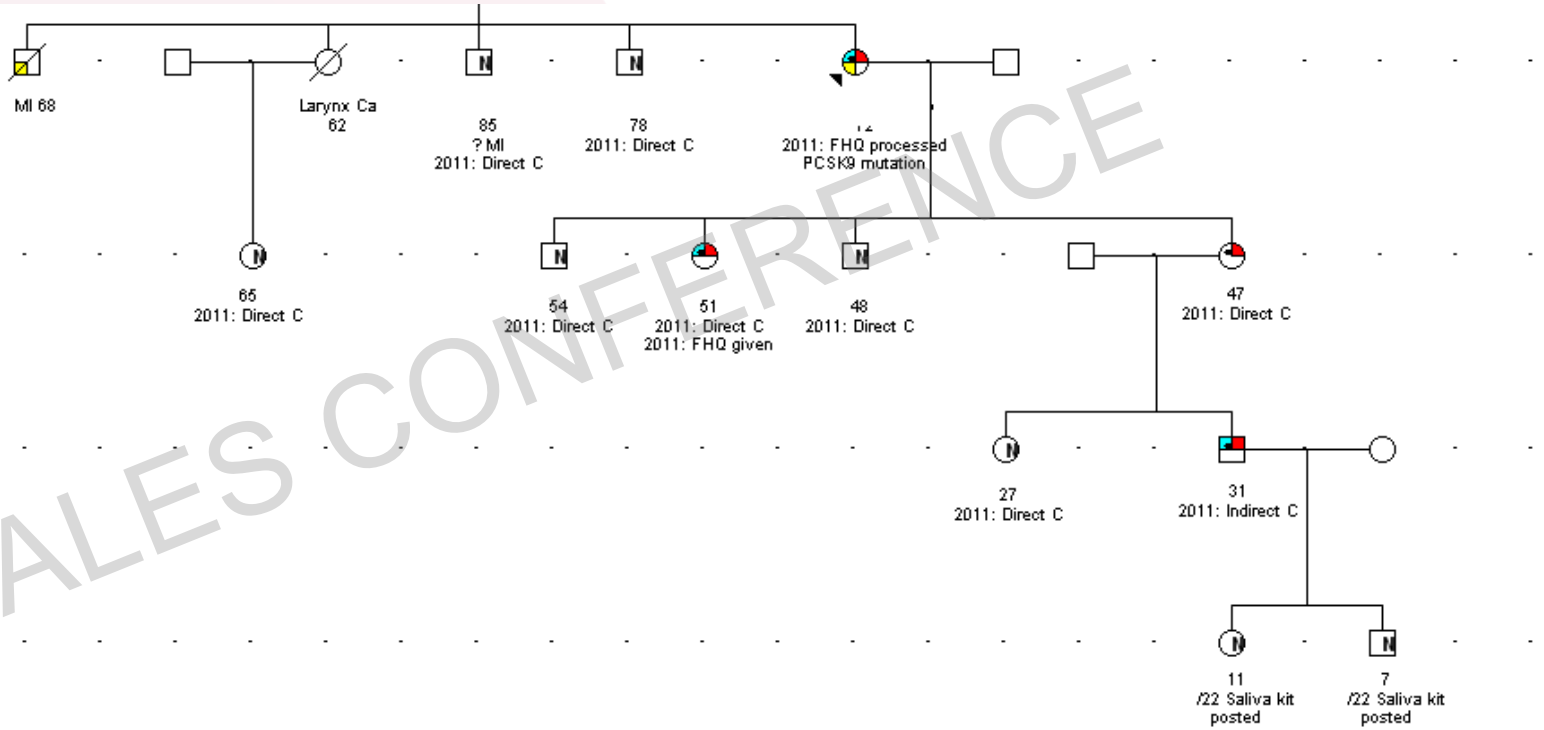

ANGIO/PCI REPORT

DATE OF PROCEDURE: [redacted] 2022

[redacted] was transferred from the wards for PCI RCA on [redacted] 2022.

Indication -NSTEMI. Exertional chest pain. Minor trop rise of 27. Normal ECG and Echo. CTCA showed normal LM LAD and LCx but severe plaque disease prox RCA.

Background Hx

1. FH.
2. Hypothyroid.

Coronary angiogram RRA. 6 Fr sheath.
Very anxious, needle phobia. Given Midazolam 2 mg, Fentanyl 50 mcg upfront.

Date Collected	:	09/09/22	21/06/22	21/04/20	09/03/20	20/04/15
Lipid profile		[redacted]	Ref2	Ref3	Ref4	Ref5
Fasting Status	:		Random	Fasting	Fasting	Fasting
Cholesterol	:		9.8	6.1	10.9	10.2
Triglyceride	:		0.9	1.0	0.6	0.6
HDL Cholesterol	:		0.7 L	0.8 L	1.3	1.1
NHDL	:		9.1	5.3	9.6	
HDLRAT	:		14.0	7.6	8.4	9.3
LDL Cholesterol	:		8.7	4.8	9.3	8.8

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CTCA, computed tomography coronary angiography; ECG, electrocardiogram; FH, familial hypercholesterolaemia; GoF, gain-of-function; HDL, high density lipoprotein; Hx, history; IHD, ischaemic heart disease; LAD, left anterior descending artery; LCx, left circumflex; LDL, low density lipoprotein; LM, left main; NHDL, non-high density lipoprotein; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; PCSK9, proprotein

Conclusions

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- Under-diagnosis of FH represents a significant missed opportunity for prevention of coronary artery disease and premature death. Some patients with undetected FH will suffer avoidable premature CVD and higher risk of early death[1]
- Genetic testing used is the gold-standard diagnostic[2]

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CVD, cardiovascular disease; FH, familial hypercholesterolaemia. 1. Mayo Clinic. Familial hypercholesterolemia: Symptoms & causes. Available from https://www.mayoclinic.org/diseases-conditions/familial-hypercholesterolemia/symptoms-causes/syc-20353755. Accessed March 2023; 2. Shah NP, et al. Cleve Clin J Med 2020;87:109-120