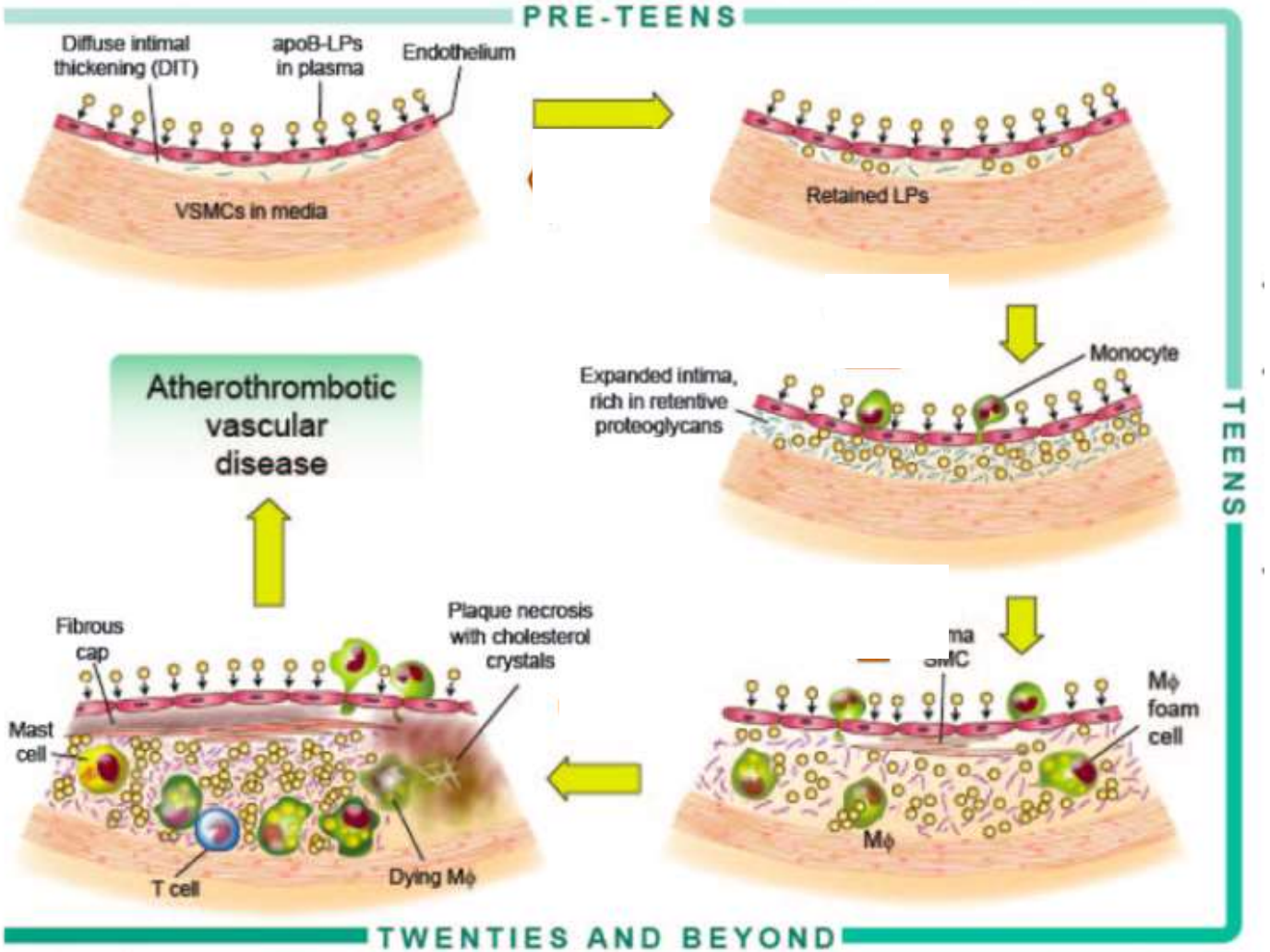
The Value of FH Genetic Diagnosis and Cascade Testing Services

- beginning to see the light

Dr Dermot Neely

Lipid Clinic, Royal Victoria Infirmary, Newcastle upon Tyne

The Response-to-Retention model of atherogenesis

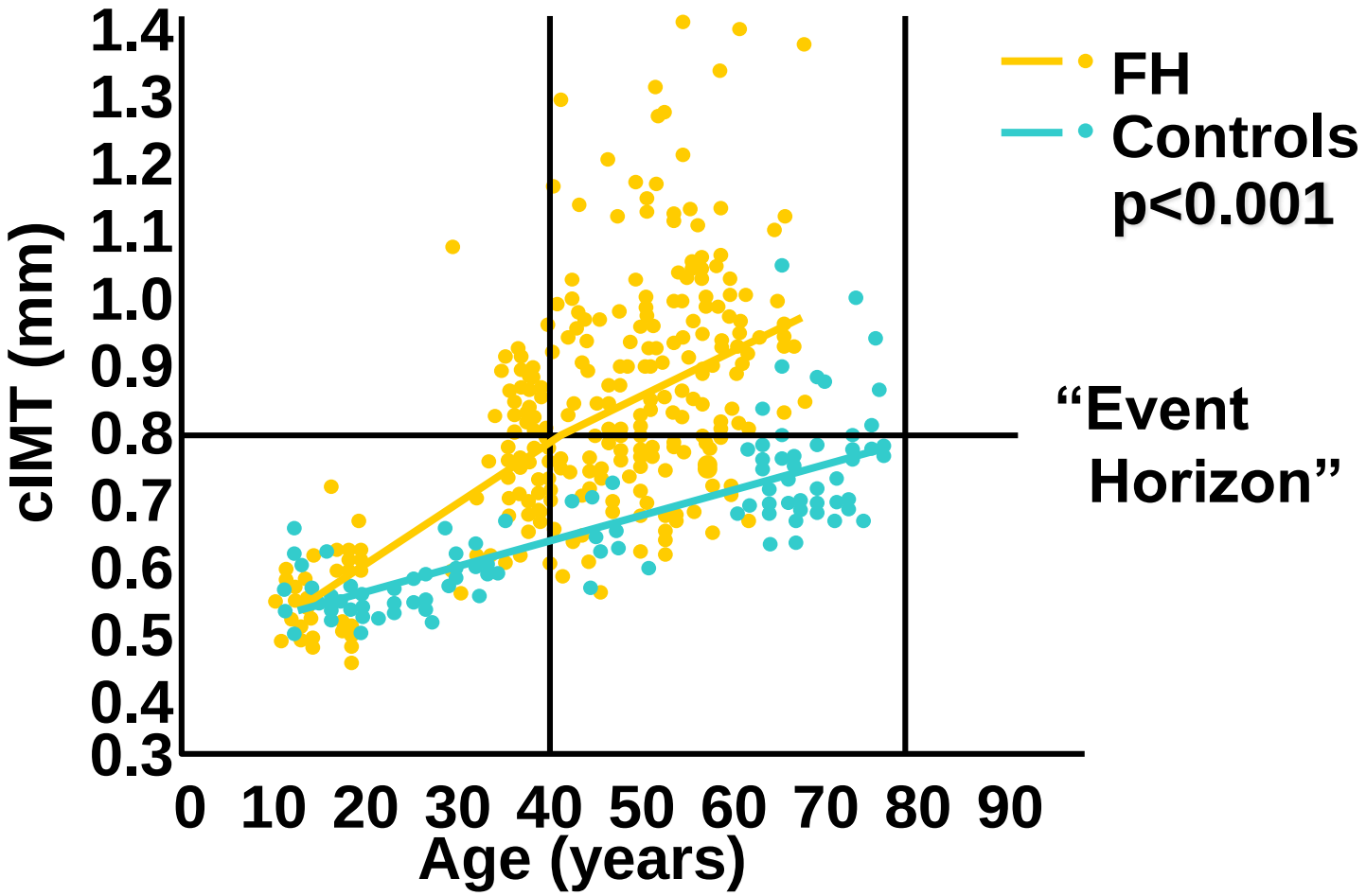


Circulation

Tabas, I. et al. Circulation 2007;116:1832-1844

Carotid atherosclerosis in Heterozygous FH

Carotid wall thickness (IMT) versus age in HeFH patients

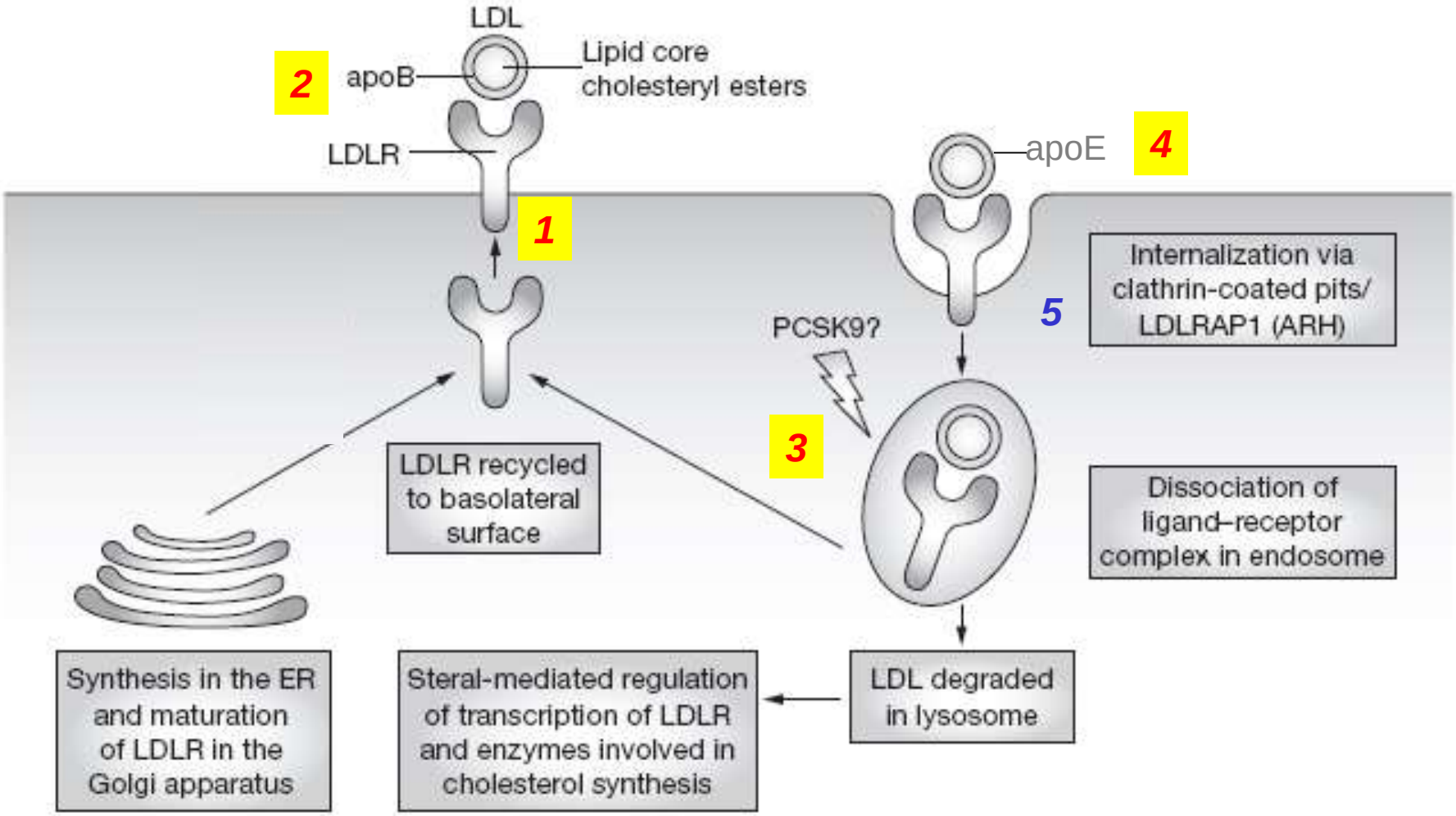


Kastelein J. data presented at EAS 2002

Familial Hypercholesterolaemia - Overview

- **FH is an autosomal dominant genetic condition that leads to doubling of LDL-cholesterol levels from soon after birth.**
  - Average LDL-cholesterol is 5.7 mmol/L in HeFH and > 13 mmol/l in HoFH
- **Lifetime burden of high LDL-cholesterol leads to dramatically increased risk of premature cardiovascular disease.**
  - >20 fold increased risk of premature myocardial infarction (MI before 60 years)
- **FH is among the most common inherited conditions:**
  - Prevalence of heterozygous FH (HeFH) is 1:200-1:300.
  - Homozygous FH is rare at 1:250,000 but has terrible consequences (MI in childhood)
  - FH affects all race/ethnic groups

FH – a monogenic disorder of the LDL-receptor pathway

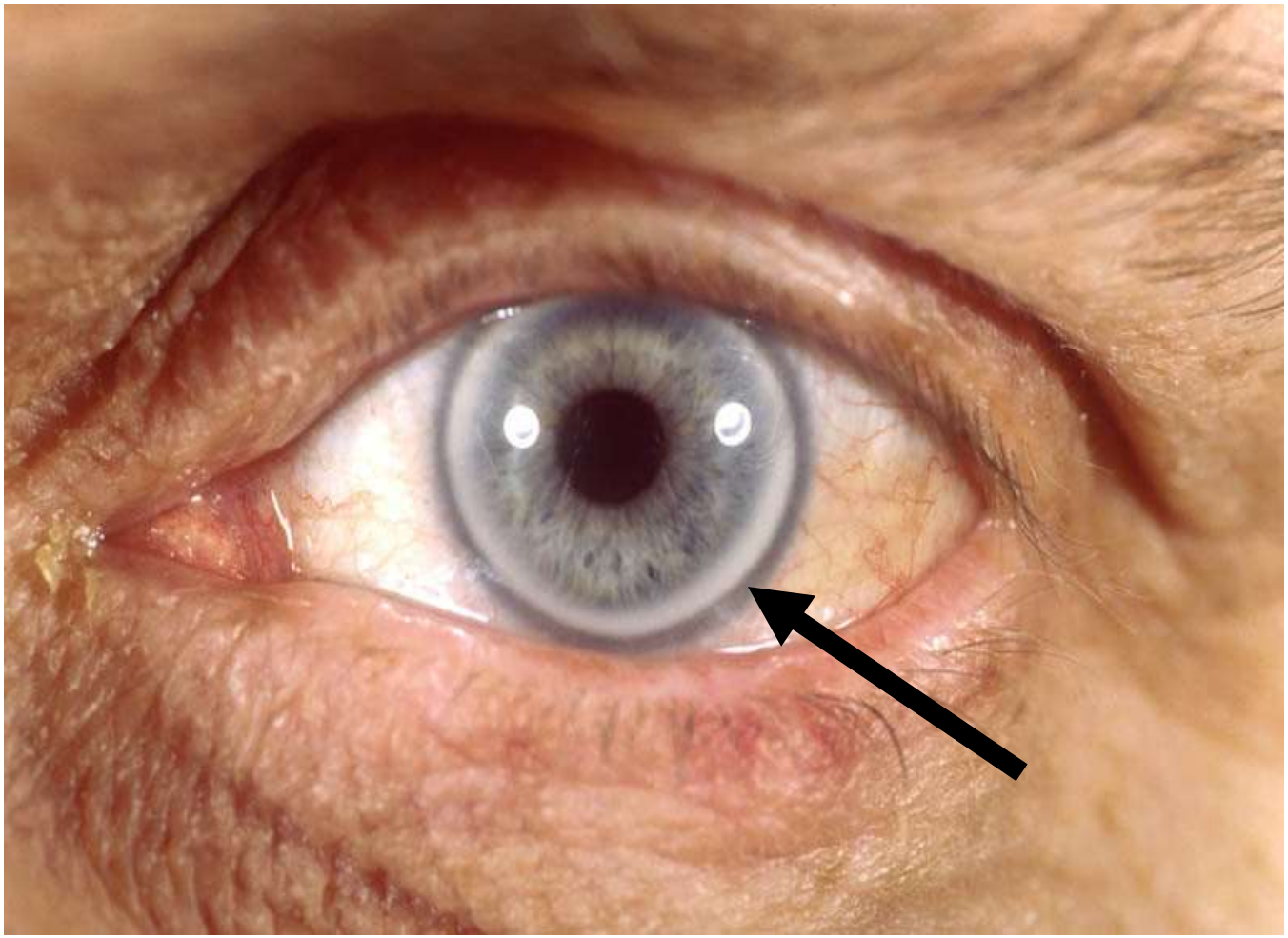


Adapated from Soutar, A Nat Clin Pract Cardiovasc Med 2006; 4:214

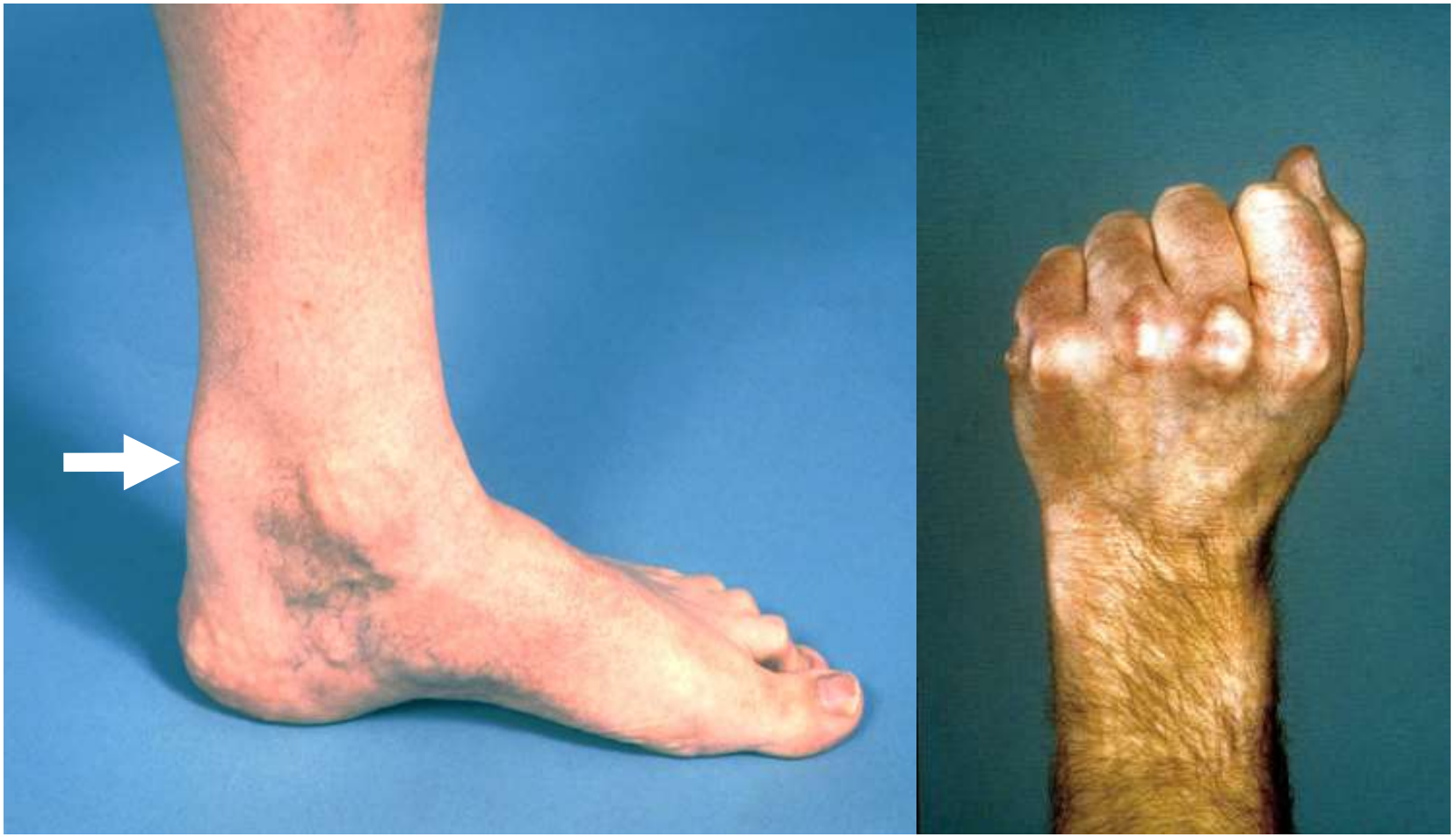
Familial Hypercholesterolaemia - Overview

- **FH can be diagnosed based on a combination of lipid levels, family history, findings on physical examination and genetic testing.**

Corneal Arcus Lipidus



Tendon Xanthoma



Diagnostic Criteria for Heterozygous FH

Simon Broome Register Criteria (UK) for HeFH in probands

1.	Total cholesterol above 7.5mmol/l or LDL cholesterol above 4.9mmol/l in an adult (levels either pre-treatment or highest on treatment) *Total cholesterol above 6.7mmol/l or LDL cholesterol above 4.0mmol/l in a child aged under 16 years*
2.	Tendon xanthomas in patient, 1st degree relative (parent, sibling, child), or 2nd degree relative (grandparent, uncle, aunt)
3.	DNA-based evidence of an LDL receptor mutation, familial defective apo B-100, or a PCSK9 mutation.
4.	Family history of premature myocardial infarction : below age of 50 years in 2nd degree relative or below age 60 years in 1st degree relative
5.	Family history of raised total cholesterol: above 7.5mmol/l in adult 1st or 2nd degree relative *or above 6.7mmol/l in child or sibling aged under 16 years.*

FH "definite" if 1 + (2 or 3) are present, "possible" if 1 + (4 or 5)

Familial Hypercholesterolaemia - Overview

- **FH can be diagnosed based on a combination of lipid levels, family history, findings on physical examination and genetic testing.**
- **FH is treatable**
  - With early diagnosis and inexpensive statin therapy, excess CVD risk is eliminated

FH – natural history

Age (years)	♂ % CHD	♀ % CHD
<30	5	0
30-39	22	2
40-49	48	7
50-59	80	51
60-69	100	75

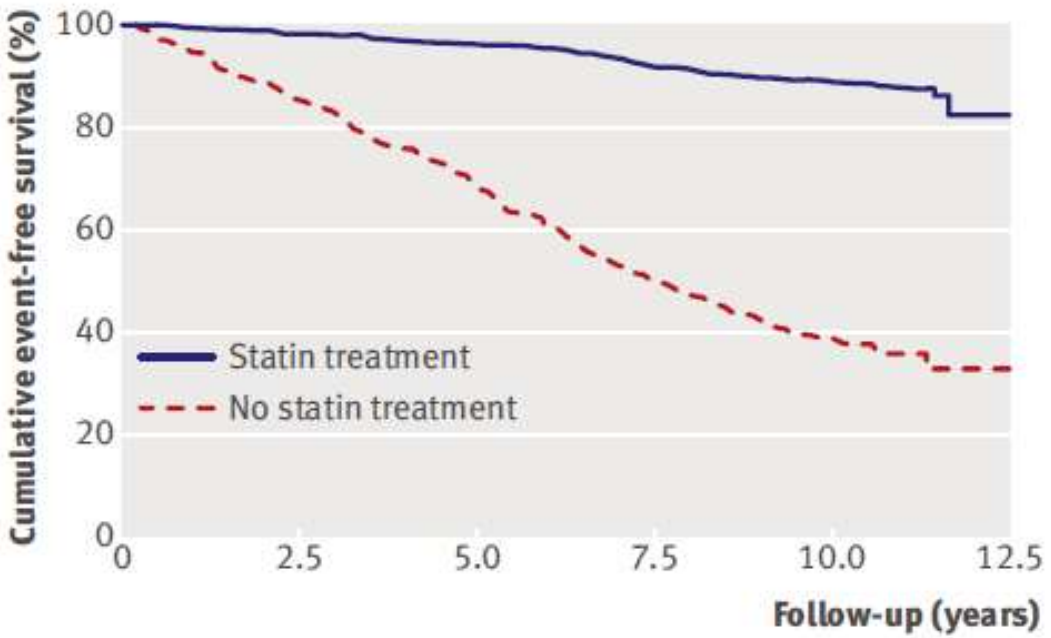
BMJ

RESEARCH

Efficacy of statins in familial hypercholesterolaemia: a long term cohort study

Jorie Versmissen, researcher,[1] Daniëlla M Oosterveer, researcher,[1] Mojgan Yazdanpanah, epidemiologist,[1] Joep C Defesche, senior researcher,[2] Dick C G Basart, clinician,[3] Anho H Liem, clinician,[4] Jan Heeringa, statistician,[5] Jacqueline C Witteman, professor of epidemiology,[5] Peter J Lansberg, clinician,[2] John J P Kastelein, professor of vascular medicine,[2] Eric J G Sijbrands, associate professor[1]

Fig 2 | Kaplan-Meier curve estimates of cumulative coronary heart disease-free survival among patients with familial hypercholesterolaemia according to statin treatment (P<0.001 for difference)

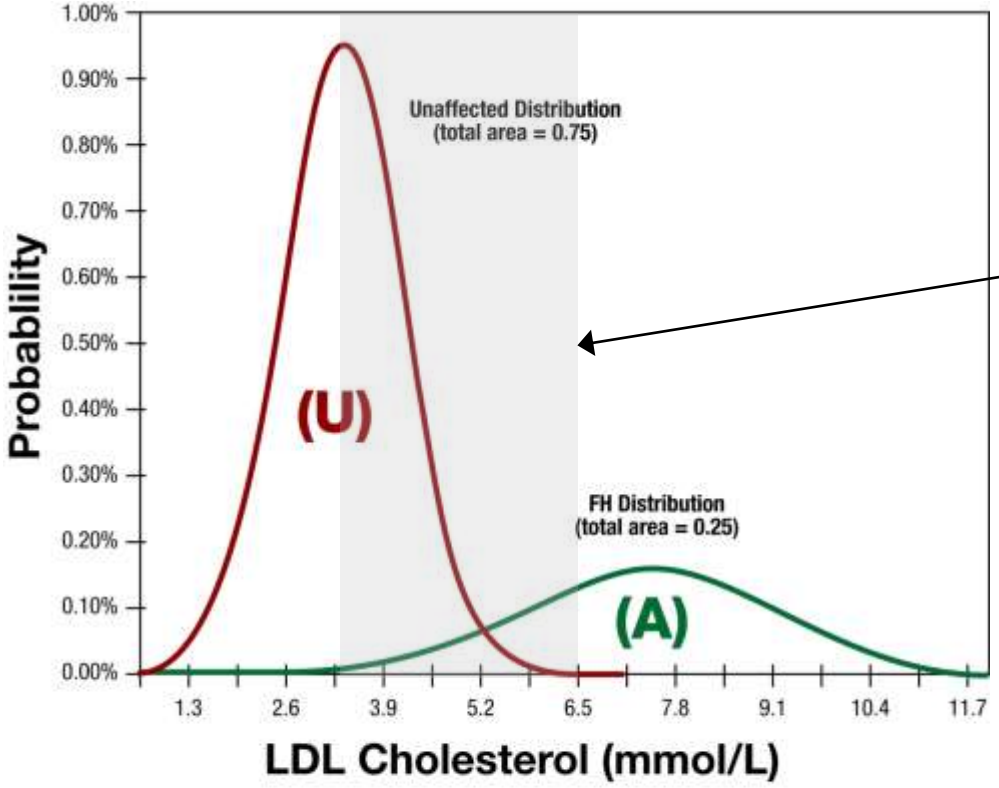


Vermissen J et al ; BMJ (2008) 337: 2423

Familial Hypercholesterolaemia - Overview

- **FH can be diagnosed based on a combination of lipid levels, family history, findings on physical examination and genetic testing.**
- **FH is treatable**
  - With early diagnosis and inexpensive statin therapy, excess CVD risk is eliminated
- **FH is massively underdiagnosed and undertreated.**
  - There are around 240,000 people in England with FH but only 10% have been diagnosed.
- **Because of the dominant inheritance of the disease, when one person in a family is diagnosed with FH, it is vitally important to screen the related family members (known as “cascade testing”)**

Second Degree Relatives of FH Proband - the LDL Cholesterol Overlap



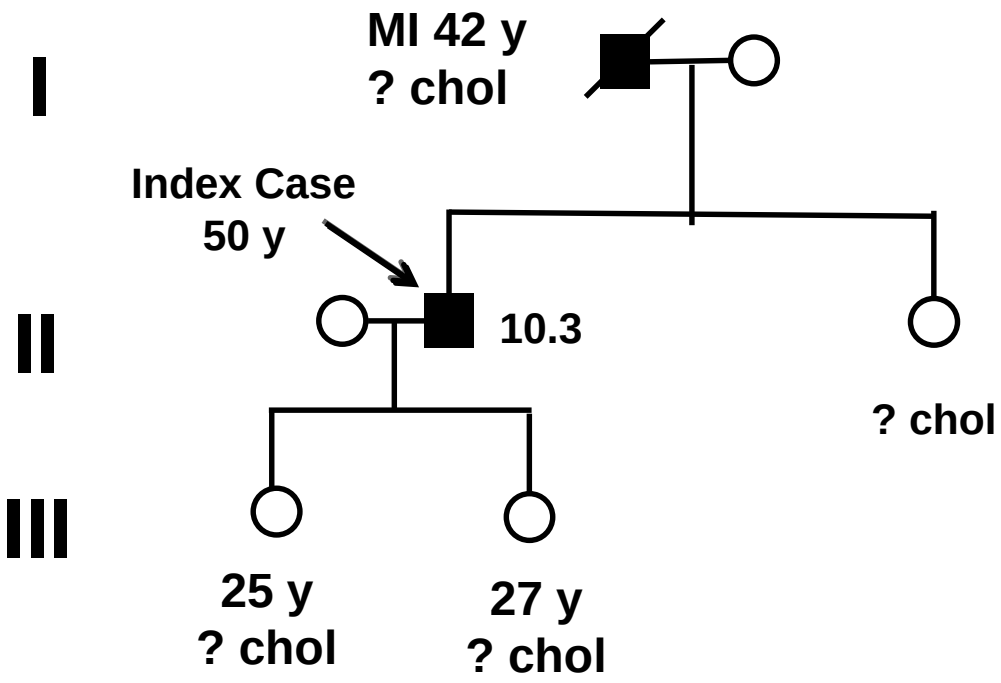
The "grey zone"

Second degree relatives 1 in 4 chance of being affected

Affected (A) and Unaffected (U)

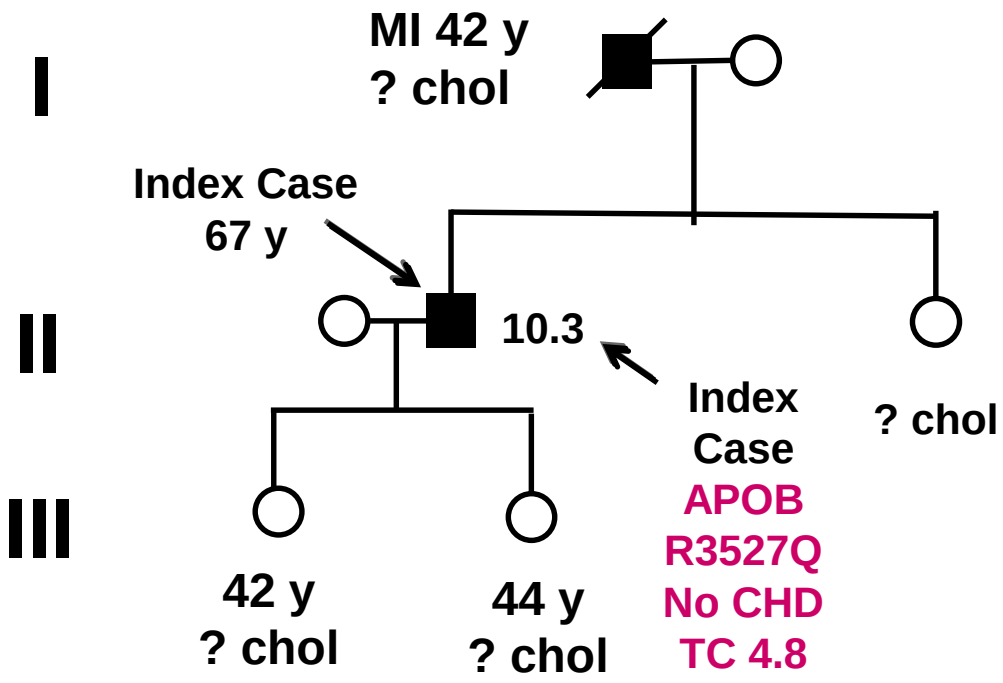
Finding a FH causing mutation eliminates the "grey zone"

Family History 1990



First degree relatives **1 in 2 chance of being affected**

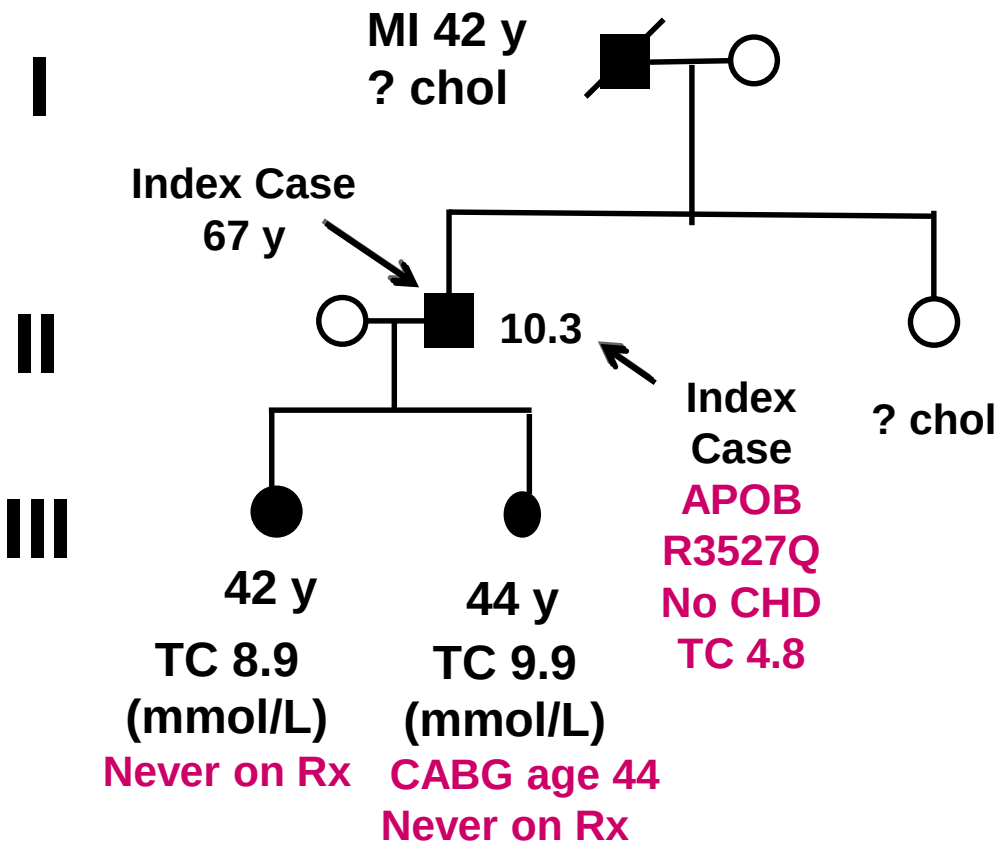
Family History Revisited 2007



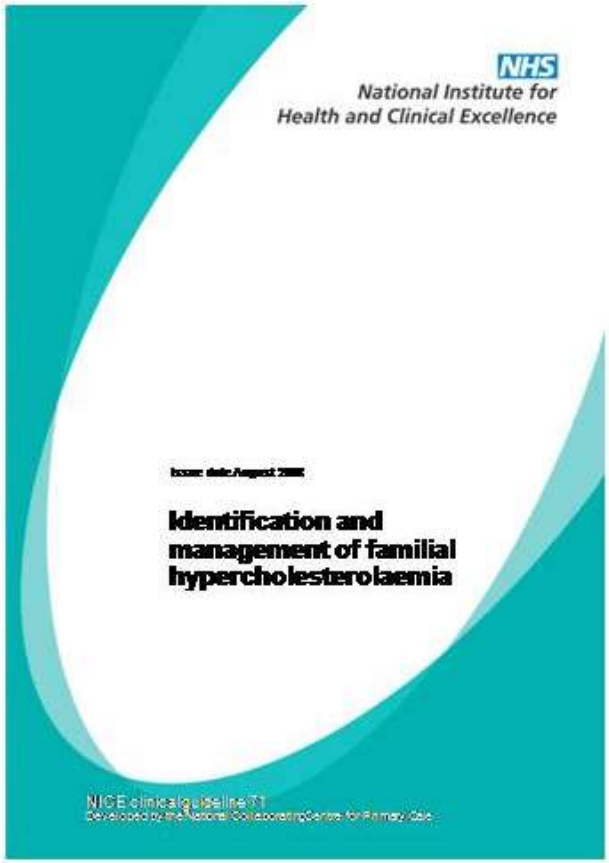
First degree relatives **1 in 2 chance of being affected**

Second degree relatives **1 in 4 chance of being affected**

Family History Revisited 2007



NICE FH Guideline (CG71 August 2008)



Royal College General Practictioners Core Team
Kathy DeMott, Leo Nherera, Meeta Kathoria, Beth Shaw, Gill Richie, Vanessa Nunes, Nancy Turnball

Guideline Development Group (GDG)
GP Chair: Dr Rubin Minhas
Lead Advisor : Prof Steve Humphries
Lipidologists : Prof Andrew Neil, Dr Mary Seed, Dr Ian McDowell
Nurse Specialist/Genetic Counsellor : Ms Melanie Watson
Dietician : Ms Helen Stracey
Epidemiologist : Prof Margaret Thorogood
Paediatrician : Dr Philip Lee
GP : Dr Nadeem Qureshi
Patient Representatives : Dawn Davies, Phil Rowlands
Co-opted Experts : Tony Weirzbicki, Helen Williams, Aileen Parke, Richard Wray, Mahmoud Barbir, Anneke Lucassen

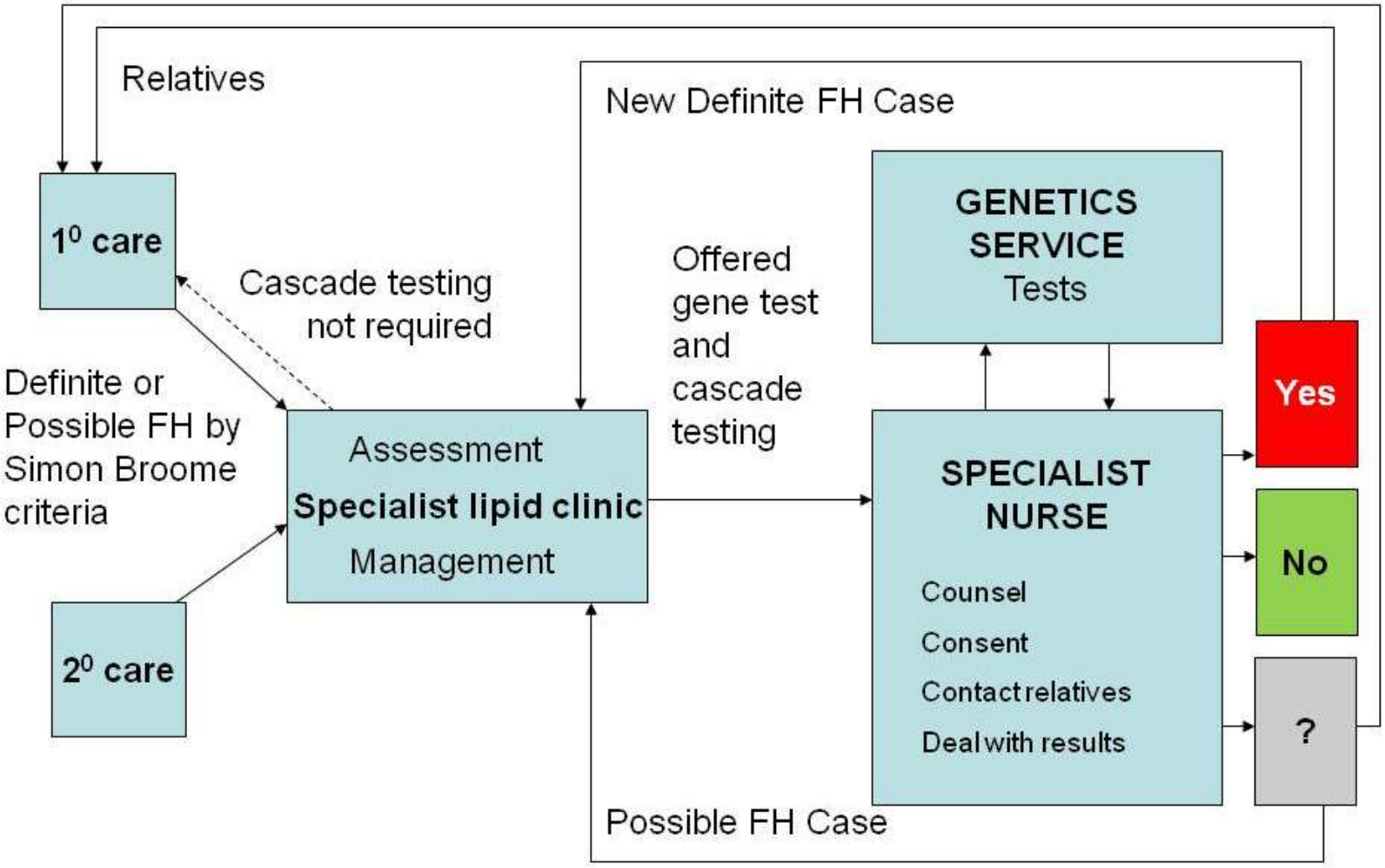
Wierzbicki et al BMJ 2008 Aug 27 337:1095

"the cascade testing model for diagnosing FH is very cost-effective, with an estimated ICER (incremental cost effectiveness ratio) of £2,700 per QALY (quality adjusted life year); well below the NICE cost effectiveness threshold of £20-30,000/QALY"

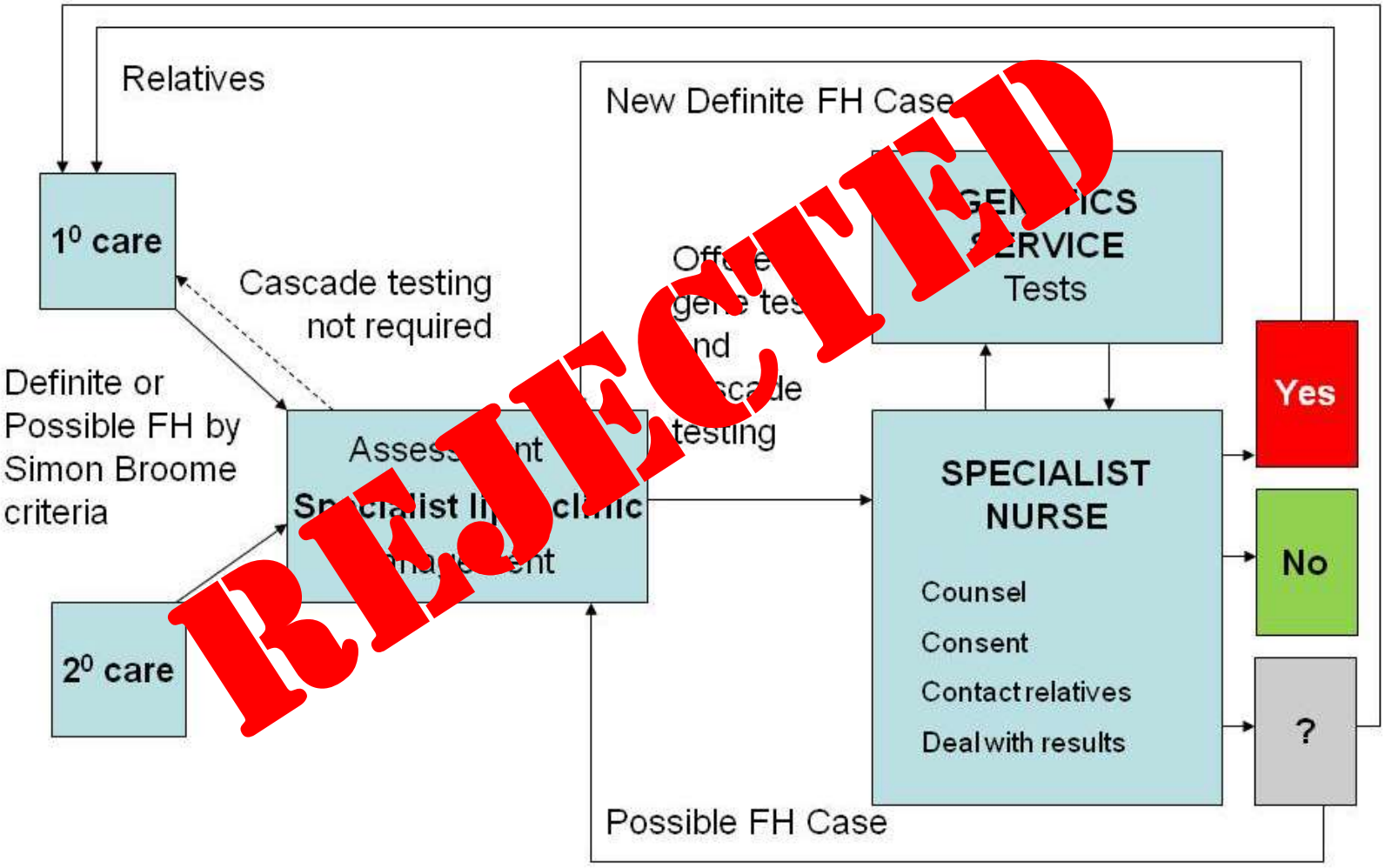
FH in North East 2009

- **Adult specialist lipid clinics well established in 6 Trusts**
  – Durham, Gateshead, Hartlepool, Newcastle, Northumbria, Sunderland
- **Adult FH outpatients also seen in Carlisle, Middlesbrough**
- **Paediatric Lipid clinics in 2 Trusts**
  – Newcastle and Sunderland
- **Regional experience of FH Genetic Diagnosis and Cascade Testing**
  - Newcastle Clinic and Regional Genetics participated in National Pilot Study of FH Genetic Diagnosis and Family Cascade Testing 2005-2008, 145 probands genotyped
- **Regional Genetics Service agree to continue FH mutation testing**
  - continue to accept requests for of relatives of FH probands with known mutations.
- **Specialist Lipid Clinics Network created in 2008**
  - agreed NICE CG71 compliant FH identification and management pathway

North East FH Service Proposal 2009



North East FH Service Proposal 2009



Why has England failed to implement the NICE FH Guideline?

- **FH not a national priority ("flogging vs hanging")**
- **Insufficient payback within 3 years**
- **"We don't want to go looking for people"**
- **"potentially thousands with cholesterol >7.5"**
- **FH too common for specialised commissioning**
- **Genetic testing expensive, growing rapidly**
- **No English PCTs have commissioned FH services**
- **Ironically, FH is a national priority in Wales, Scotland and Northern Ireland and cascade testing programmes based on genetic diagnosis have been launched**

"..a national disgrace"- Prof John Deanfield, Chair, JBS3

HEART UK
THE CHOLESTEROL CHARITY

Saving lives, saving families

The health, social and economic advantages of detecting and treating familial hypercholesterolaemia (FH)

Heart UK. Saving lives, saving families: the health, social and economic advantages of detecting and treating familial hypercholesterolaemia (FH). Heart UK, 2012.

“High intensity treatment will mean 101 cardiovascular deaths are avoided per 1,000 FH patients (aged 30 to 85 years) treated, when compared with no treatment”

“The UK could save £378.7 million from cardiovascular events avoided if all (100 per cent) relatives of FH index cases are identified and treated optimally over a 55 year period, or £6.9m per year.”

Heart UK. Saving lives, saving families: the health, social and economic advantages of detecting and treating familial hypercholesterolaemia (FH). Heart UK, 2012.

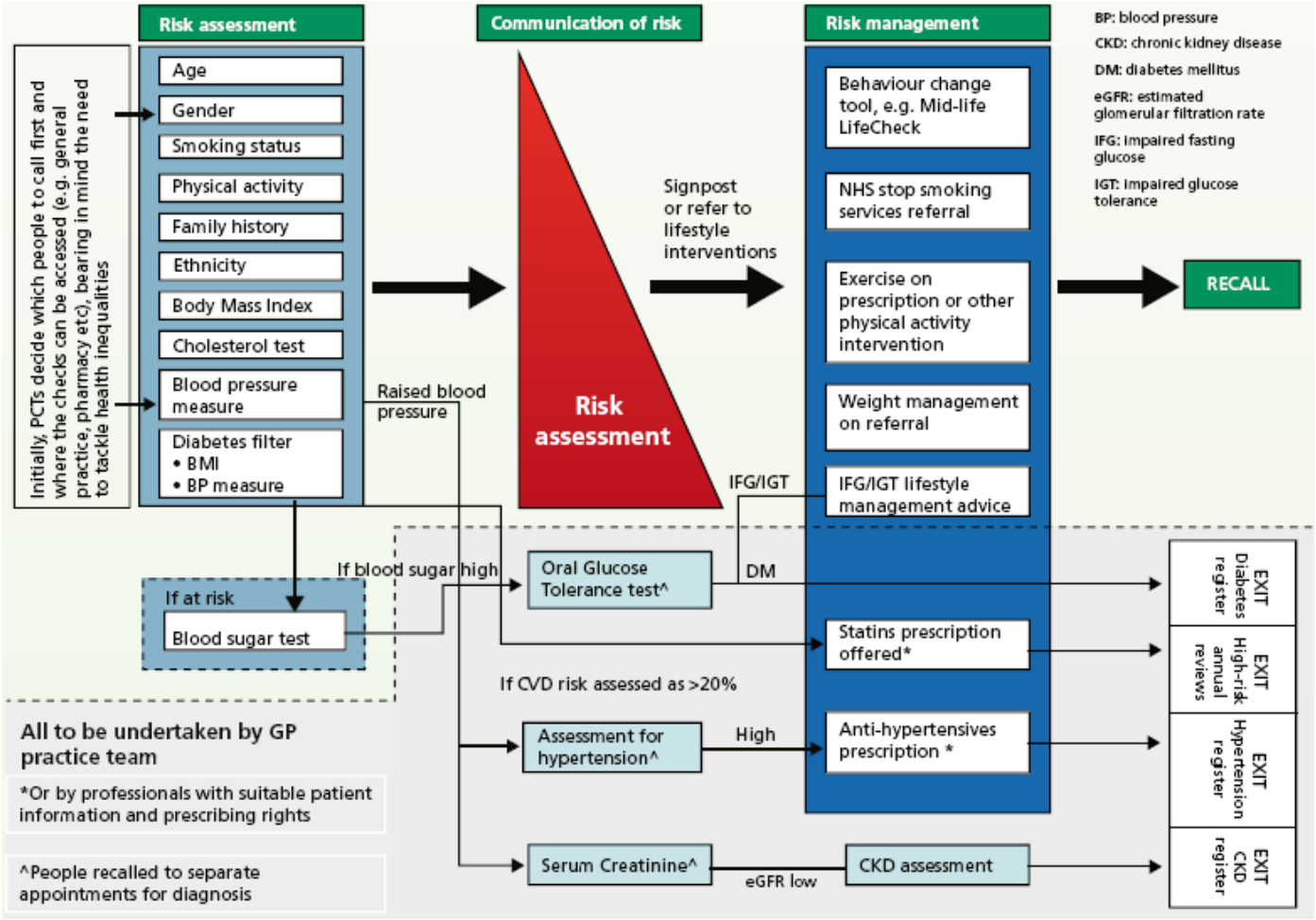
What is the value of developing FH services?

- **Patients - Early diagnosis of a life threatening genetic condition. Getting the right medication as early as possible. Information and support from healthcare specialists and from other FH patients at patient support groups**

- **Local GPs and CCGs - More accurate knowledge about the prevalence of FH in the region. Ability to provide appropriate care to as many patients as possible. Ability to prevent serious symptoms with early treatment.**

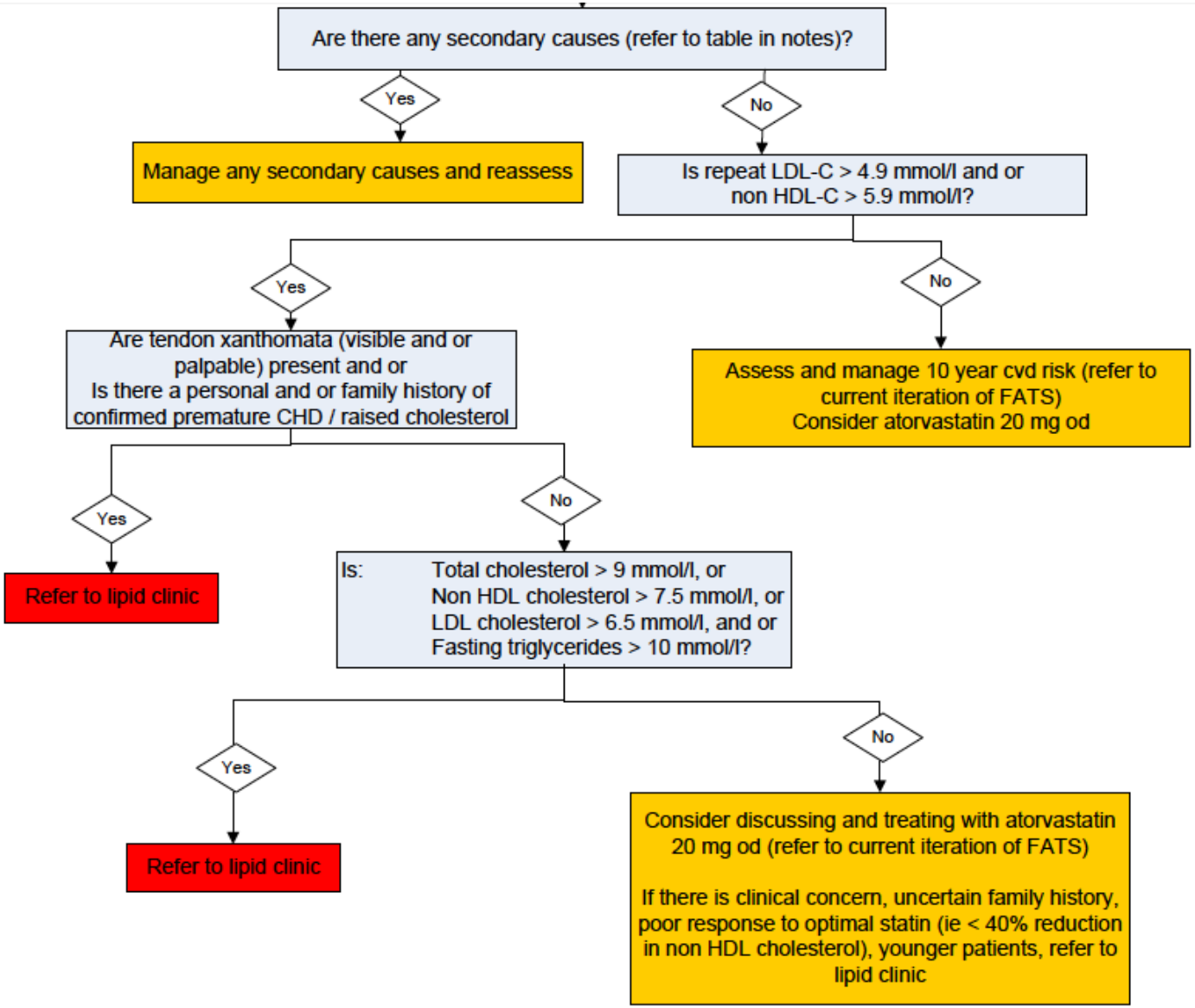
- **Local NHS Trusts - An increase in early FH diagnoses should lead to a reduction in premature cardiovascular events and a reduced burden on cardiac services.**

National Health Checks Program

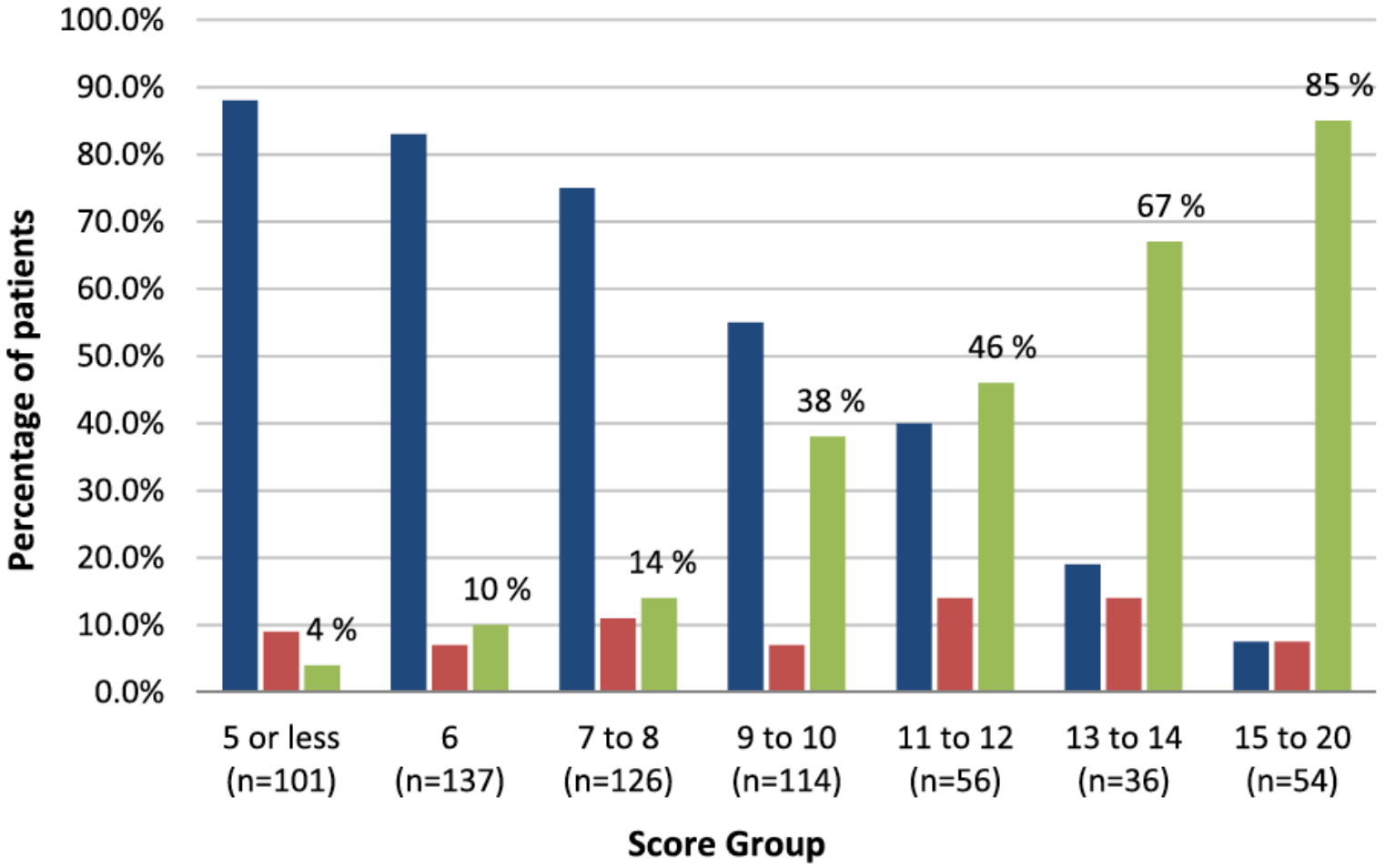


Of those >40 years, approximately 4% have total cholesterol >7.5mmol/L, of whom 1 in 20 will have undiagnosed FH and 3-5 relatives with undiagnosed FH } **~5,000 in our region remain undiagnosed**

Total cholesterol > 7.5 mmol/l and/or LDL cholesterol > 4.9 mmol/l (contd)



FH Phenotype Score for Identification of Proband – part of the solution?



NORTHERN GENETICS SERVICE

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

FAMILIAL HYPERCHOLESTEROLAEMIA DNA ANALYSIS REQUEST FORM

Completion of this form is required as a prerequisite to molecular analysis

Patient Surname:	Forename:		Consultant name and clinic address
Date of birth dd/mm/yyyy:	...../...../.....	Male/ Female	Patient postcode:
NHS Number:			Sample Collection Date:...../...../..... dd/mm/yyyy
Family file number:	Ethnic origin:		Consent Obtained Testing Y / N Storage Y / N

PROBAND WITH UNKNOWN MUTATION Tick if required ☐

Dutch Lipid Clinics Network Score

A. Family History				
Enter Number of relatives at 50% risk: ☐		Number of relatives at 25% risk		
I.	First degree relative with premature CHD and/or CVD*	Y / N		
II.	First degree relative with LDL cholesterol >5.5	Y / N	1	
III.	First degree relative with xanthoma or corneal arcus	Y / N		
IV.	First degree relative age <18 with LDL cholesterol >3.9	Y / N	2	
*Premature CHD and/or CVD in men <55 years, women <60 years				
B. Personal History				
I.	History of premature CHD (M <55, F <60)	Y / N	2	
II.	History of premature PAD or CEVD	Y / N	1	
C. Physical Examination				
I.	Tendon xanthomas	Y / N	6	
II.	Premature corneal arcus (<45 years)	Y / N	4	
D. Fasting LDL cholesterol with triglycerides <2.3**				
**LDL cholesterol for calculation of the score is highest without drug treatment.				
I.	LDL cholesterol >8.5	Y / N	8	
II.	LDL cholesterol 6.5 – 8.4	Y / N	5	
III.	LDL cholesterol 5.0 – 6.4	Y / N	3	
IV.	LDL cholesterol 4.0 – 4.9	Y / N	1	
Add HIGHEST score from each of domains A + B + C + D =		Total		

Genetic studies can be ordered with a score of >6. *(index cases >18 years only)*

Enter fasting lipid profile results used for diagnosis

Total cholesterol (mmol/L)		Triglycerides (fasting) (mmol/L)	
HDL-cholesterol (mmol/L)		LDL-cholesterol (mmol/L)	
Lipoprotein(a)(ifknown) (mg/L)			

The North East Lipid Clinics Network

The lipid clinics will:

- **Confirm the clinical diagnosis of FH or other disorder**
- **Provide lifestyle and dietetic advice**
- **Start and/or titrate lipid lowering drug treatment.**
- **Provide information**
- **Identify and arrange investigation if required**
- **Use DLNC score to prioritise patients for genetic testing**
- **Recommend if family cascade screening is appropriate**
- **Arrange follow up and an annual structured review**

FH Genetic Cascade Testing (GCT) Pathway

If Clinical Diagnosis of FH in Proband with DLNC ≥ 6

1. **DNA diagnosis and Family Cascade Testing offered**
2. **Proband contacted on receipt of genotyping results**
3. **Proband M+ offered appointment with FH Genetic nurse**
4. **Family pedigree recorded in PASS and used to identify relatives to be contacted (direct or indirect as preferred)**
5. **Relatives offered an appointment for Genetic Cascade Testing M+ test and fasting lipid profile in adults**
6. **If proband test negative (M-) lipid profiles in other family members advised when appropriate**
7. **Letter to GP recommending Lipid Clinic referral for M+ relatives or M- relatives with LDL-C in red/grey zone.**

First line DNA diagnosis, second line LDL-C for cascade testing

Not FH - what else could it be?

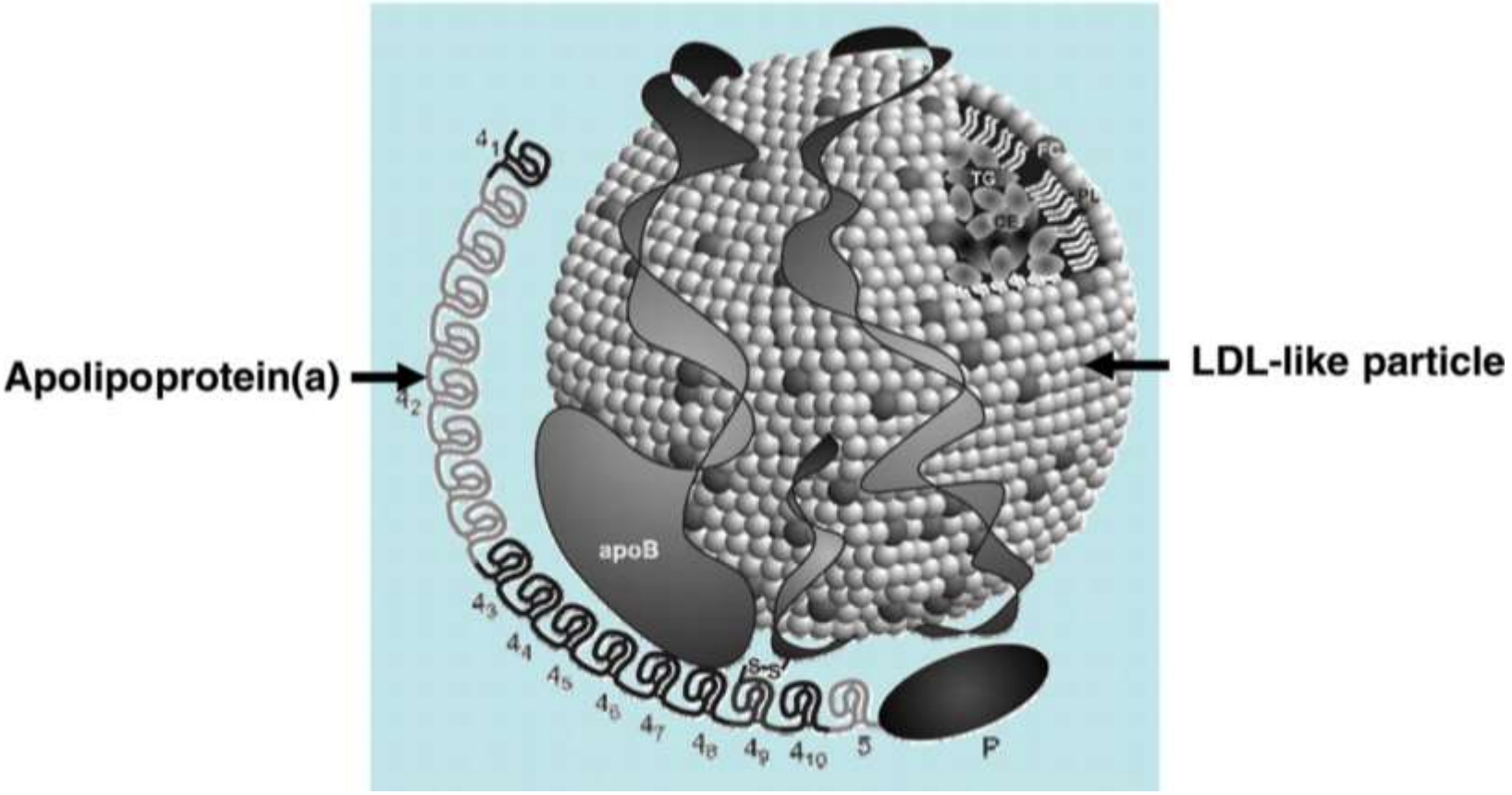
Inherited dyslipidaemias and premature CHD

	% of total CHD
Combined Hyperlipidaemia (FCH)	19%
Hyper Lp(a) (normolipidaemia)	19% (13)
Dyslipidaemia (high TG, low HDL)	15%
Hypoalphalipoproteinaemia (FHA)	4%
Hypercholesterolaemia (FH)	3%
Hypertriglyceridaemia	1%

>50% of premature CHD have a familial lipoprotein disorder

Genest JJ et al., Circulation (1992) 85: 2025-33

LPA – the 5th FH gene?

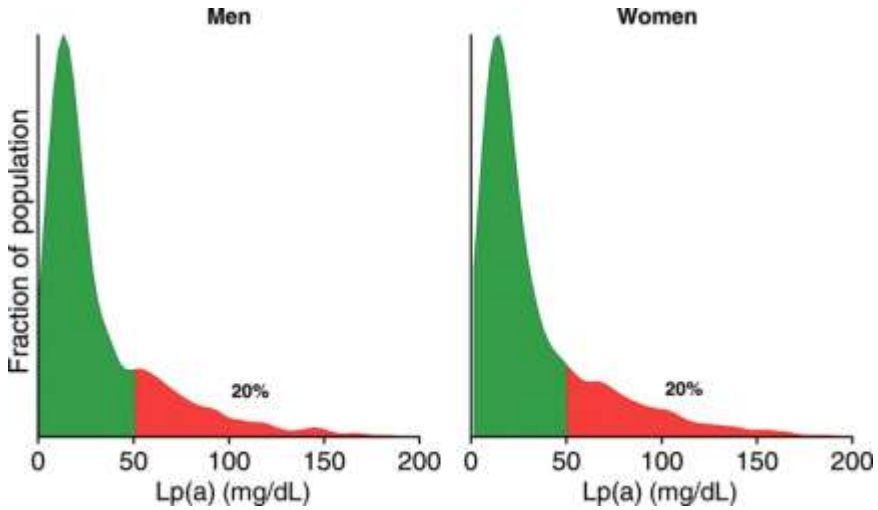


Lipoprotein(a)

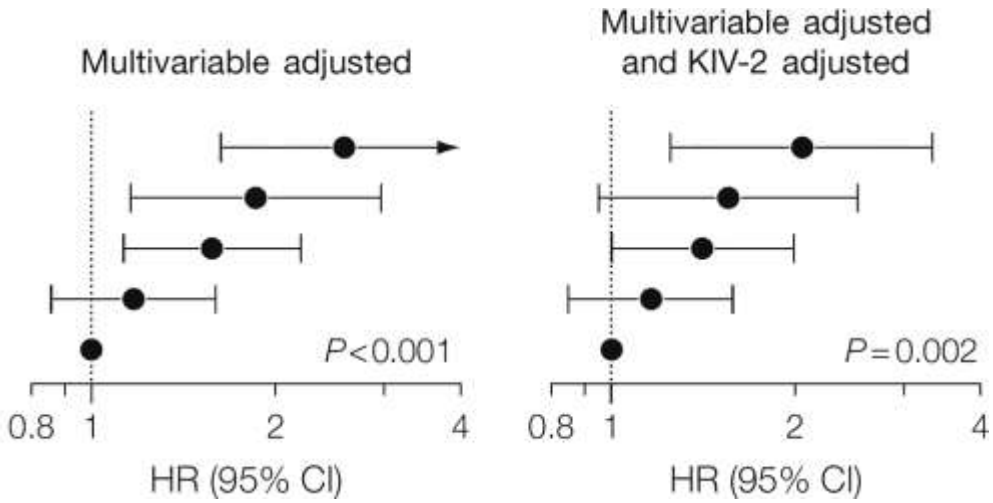
Nordestgaard B G et al. Eur Heart J 2010;31:2844-2853

European Heart Journal

Lipoprotein(a) and risk of myocardial infarction.



Lipoprotein(a)		Participants	Events
Percentile	mg/dL	(no.)	(no.)
>95th	>117	376	46
90th–95th	77–117	450	46
67th–89th	30–76	1731	155
22nd–66th	5–29	3385	241
<22nd [reference]	<5	1582	104



Nordestgaard B G et al. Eur Heart J 2010;31:2844-2853

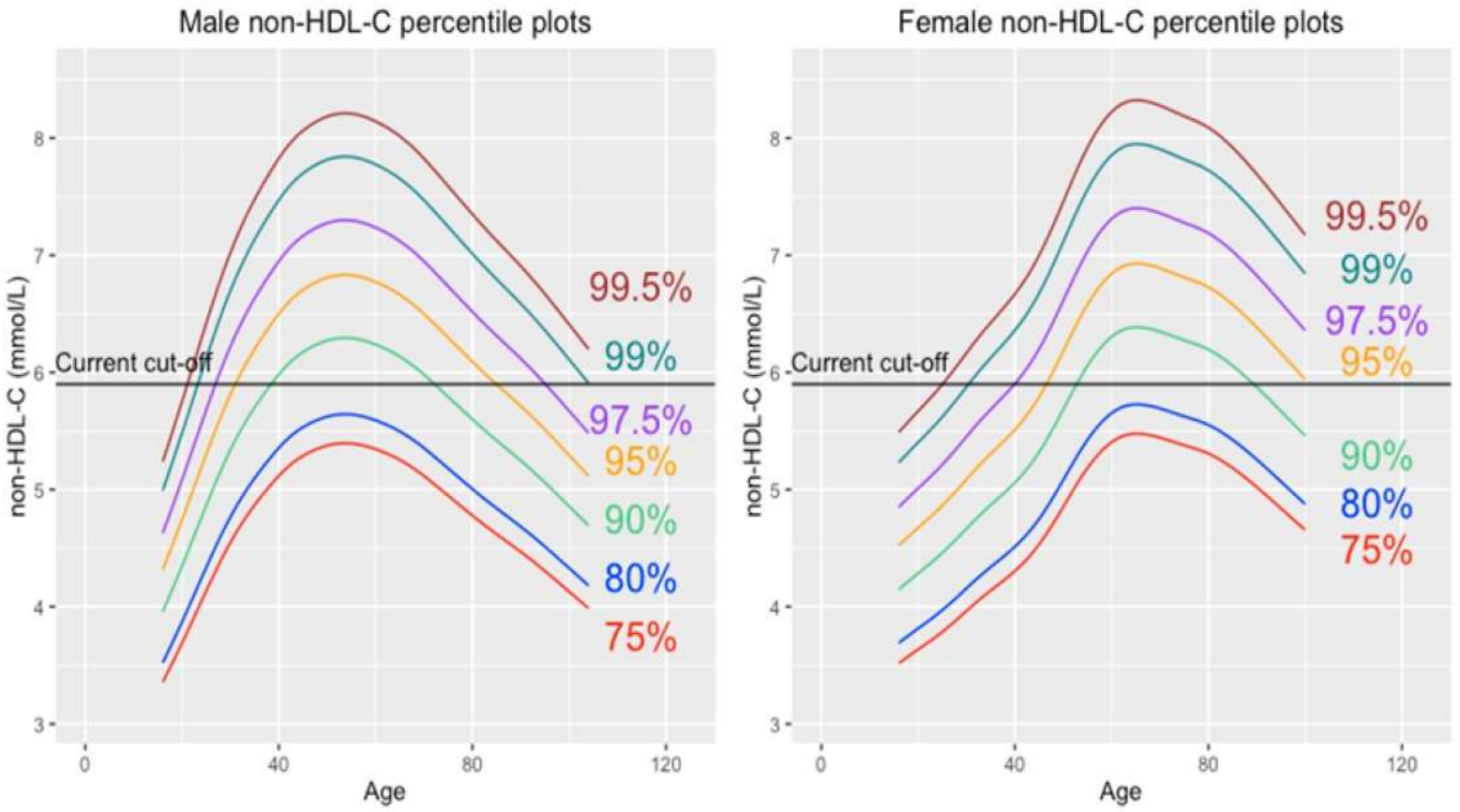
European Heart Journal

FH Case Finding and Diagnosis

- **1.1.2 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.

[NICE CG1 Update 2017]



The non-HDL-C curves (n = 26,680) show that lipid levels for males ages 40-65 and females aged 65-80. In patients with a normal fasting triglyceride of ≤1.7 mmol/L the current LDL-C cut-off (4.9mmol/L) corresponds to a non-HDL-C concentration of 5.7mmol/L. For males aged 35-64, this values lies close to the 90th percentile but is above the 99th centile for females aged 16-24.

Exclusion of Secondary Hyperlipidaemias
Key Investigations

	Tests Exclude
Renal profile (Na+,K+,Creatinine, eGFR)	Renal failure
Liver profile (TProt, Alb, ALP, ALT)	Cholestasis, M protein
Thyroid profile (TSH, FT4)	Hypothyroidism
HbA1c	Diabetes
Dipstick urinalysis, protein creatinine ratio	Nephrotic Syndrome
Also consider at baseline	
Creatine Kinase (CK)	High Baseline

When Should I Consider Specialist Referral?

After exclusion of secondary hyperlipidaemias, if:	
	Family history of premature coronary heart disease
AND	Total Cholesterol >7.5 mmol/l
OR	LDL-C > 4.9 mmol/l
	No family history premature coronary heart disease
AND	Total Cholesterol >9.0
OR	Non-HDL-Cholesterol > 7.5
OR	Triglycerides > 10 mmol/l (12 hour fasting; urgent if >20)
Above these thresholds:	
	Clinical suspicion of FH or FCH
	Cardiovascular risk tables do not apply

Summary

- The North East CVD and Lipid Clinic networks, supported by the CCG Forum have successfully established a region-wide FH service
- Excellent progress against QS41 has been achieved with AHSN and CCG investment in genetic testing and BHF support for two FH cascade testing nurses, service now fully funded by CCGs
- Use of Dutch Lipid Clinics Network Score (DLCNS) has been used to manage demand and maintain efficiency of genetic testing
- The increase in the activity of adult and paediatric lipid clinic services has been managed through tariff
- A proven, dedicated FH management program/registry (PASS) has been implemented for the efficient delivery of cascade screening within the network and linking with other services nationwide.
- Apheresis services, required to treat the few refractory FH heterozygotes and the rare homozygous cases (predicted 1-2 per million) have been established but biologic therapies (PSCK9i) may have helped reduce number requiring apheresis.