



Cost effectiveness of cascade testing for familial hypercholesterolaemia, based on data from familial hypercholesterolaemia services in the UK

Marion Kerr¹, Robert Pears², Zofia Miedzybrodzka³, Kate Haralambos⁴, Moyra Cather⁵, Melanie Watson⁶, and Steve E. Humphries^{7*}

Background

- In 2008, NICE published evidence-based guidelines for identification and management of FH

Updated 2017

- Recommended all Clinical FH → DNA test to confirm
- Plus DNA-based cascade testing from all index cases with a DNA confirmed diagnosis of FH.
- Plus electronic search of GP records for likely FH.



All recommendations supported by cost effectiveness analysis

Simon Broome criteria:

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

Possible FH

Definite FH

Corneal Arcus



Xanthelasma



Tendon Xanthoma

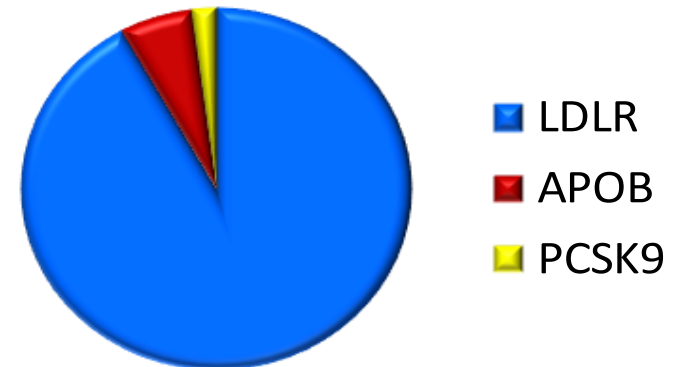


Also Dutch Lipid Clinic Criteria scoring system & US system MEDPED

What has gone wrong in FH?

FH is due to failure to clear LDL from the blood

- **LDLR** – Commonest cause > 1700 different world wide and >200 in UK
- **APOB** – One common mutation p.R3527Q
- **PCSK9** – Gain of Function - Least frequent but most severe cause
- Mutations in *LDLRAP1* → recessive FH



DNA tests for FH -

Offered by several UK NHS Diagnostic Labs eg GOSH/Bristol

- With advances in NGS all genes captured in one run
- 96 samples can be handled in one run
- Costs fallen from £6-700 to ~£250
- Time taken to report fallen from 3 months to 4-6 weeks
- Test of single mutation in relative ~ £70.

Mutation found in ~40% of clinical FH –

No mutation = polygenic hypercholesterolaemia – Talmud et al Lancet 2013

- It is Common - Frequency $\sim 1/250$ ie more than childhood diabetes!

Predict >200,000 in UK, > 1,000,000 in Europe

- It is underdiagnosed - less than 10% of predicted in UK known
- Overall we can find an FH-causing mutation in $\sim 40\%$ of index cases

Mutation +ve FH patients >>> CHD risk than those with no mutation

- 50% men \rightarrow MI by age 50yrs, and 30% of women by age 60yrs
- Statin treatment very safe and cost effective

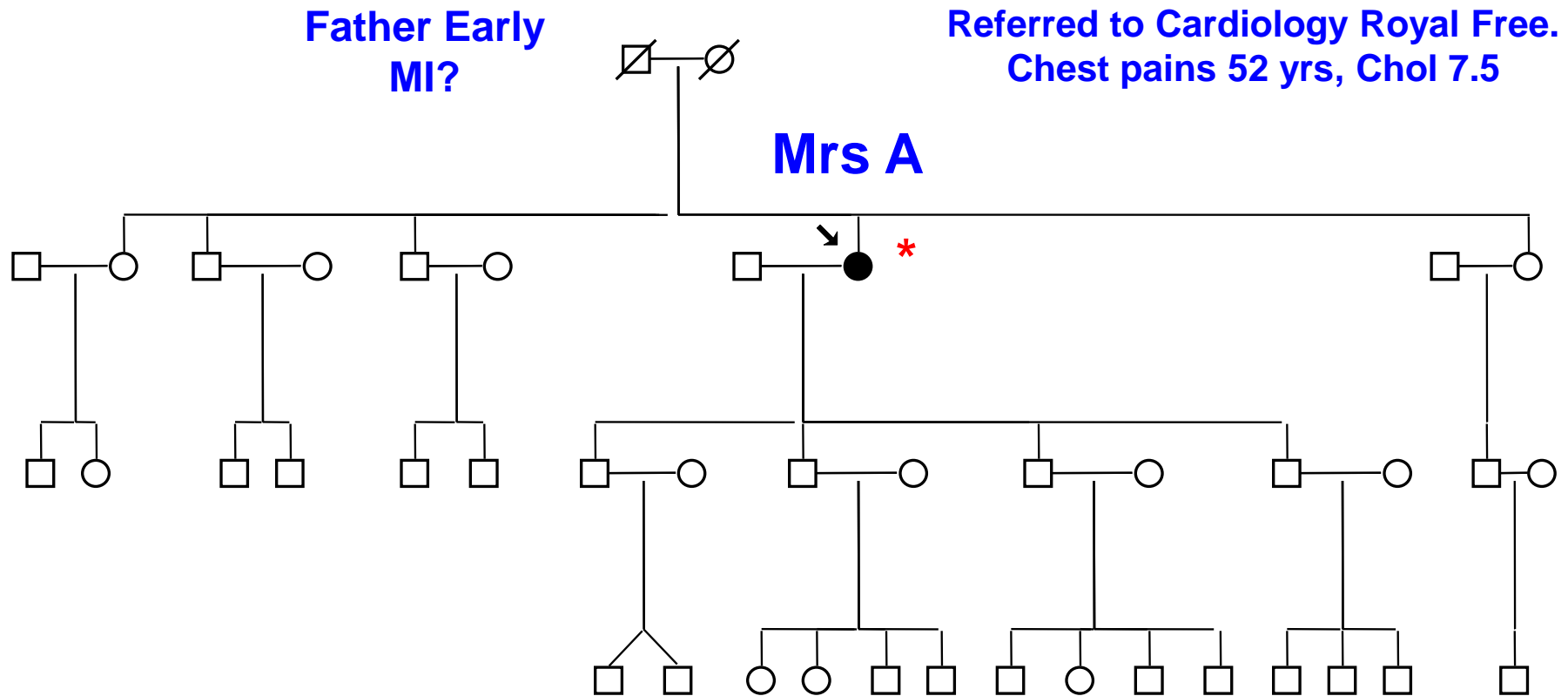
Early statin treatment \downarrow CHD risk to general population– Neil et al EHJ 2008

- Runs in Families - 50% of children of an FH parent will have FH

“Cascade” testing effective and cheap way to find more FH patients

What is Cascade Testing?

Cascade Testing in FH Family



Diagnosis: Definite monogenic FH

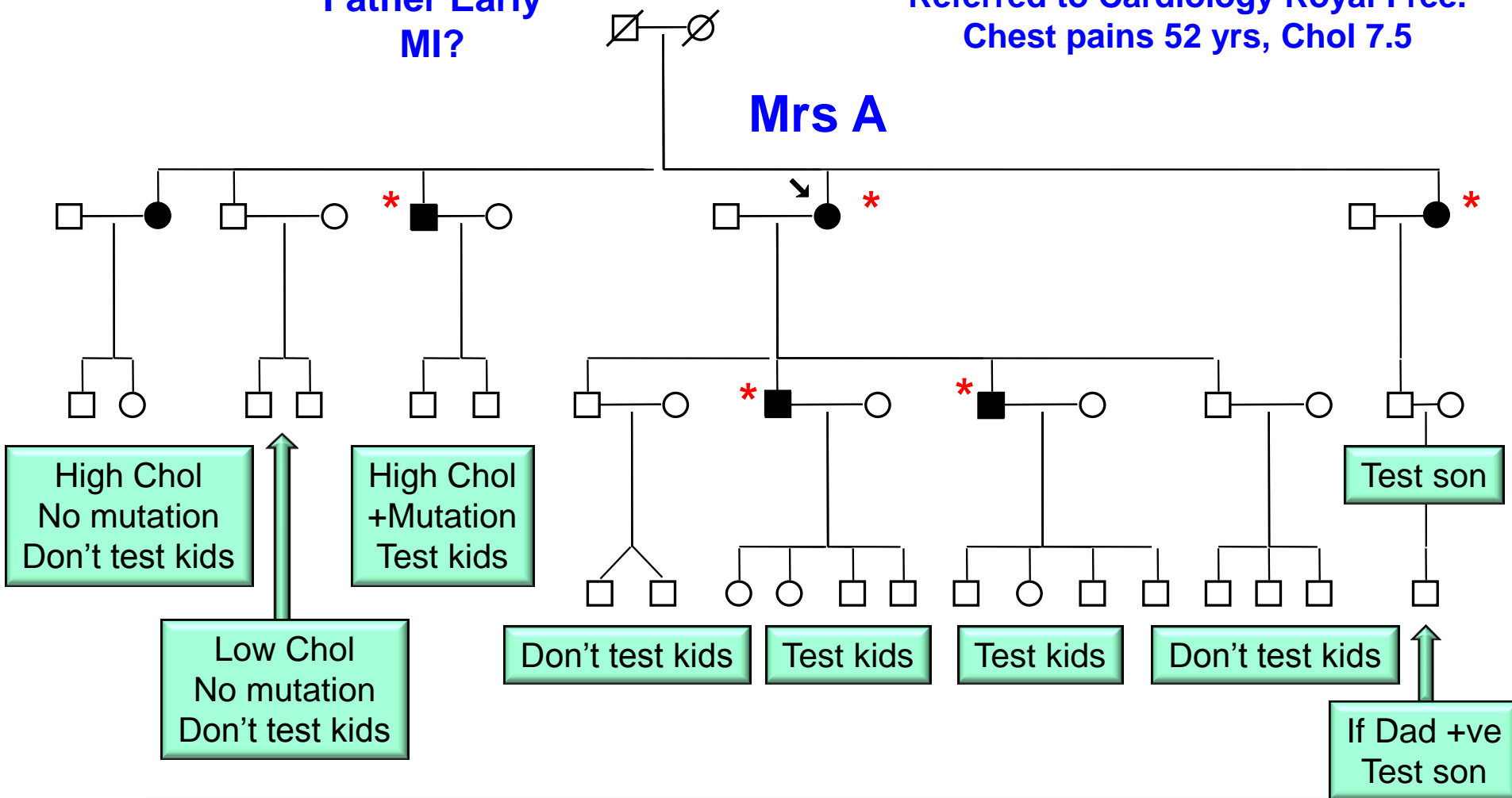
Action: Test 1st degree relatives -LDL-C and mutation

Cascade Testing in FH Family

Father Early MI?

Referred to Cardiology Royal Free.
Chest pains 52 yrs, Chol 7.5

Mrs A



Step-wise cascade maximises efficiency and minimises un-necessary testing

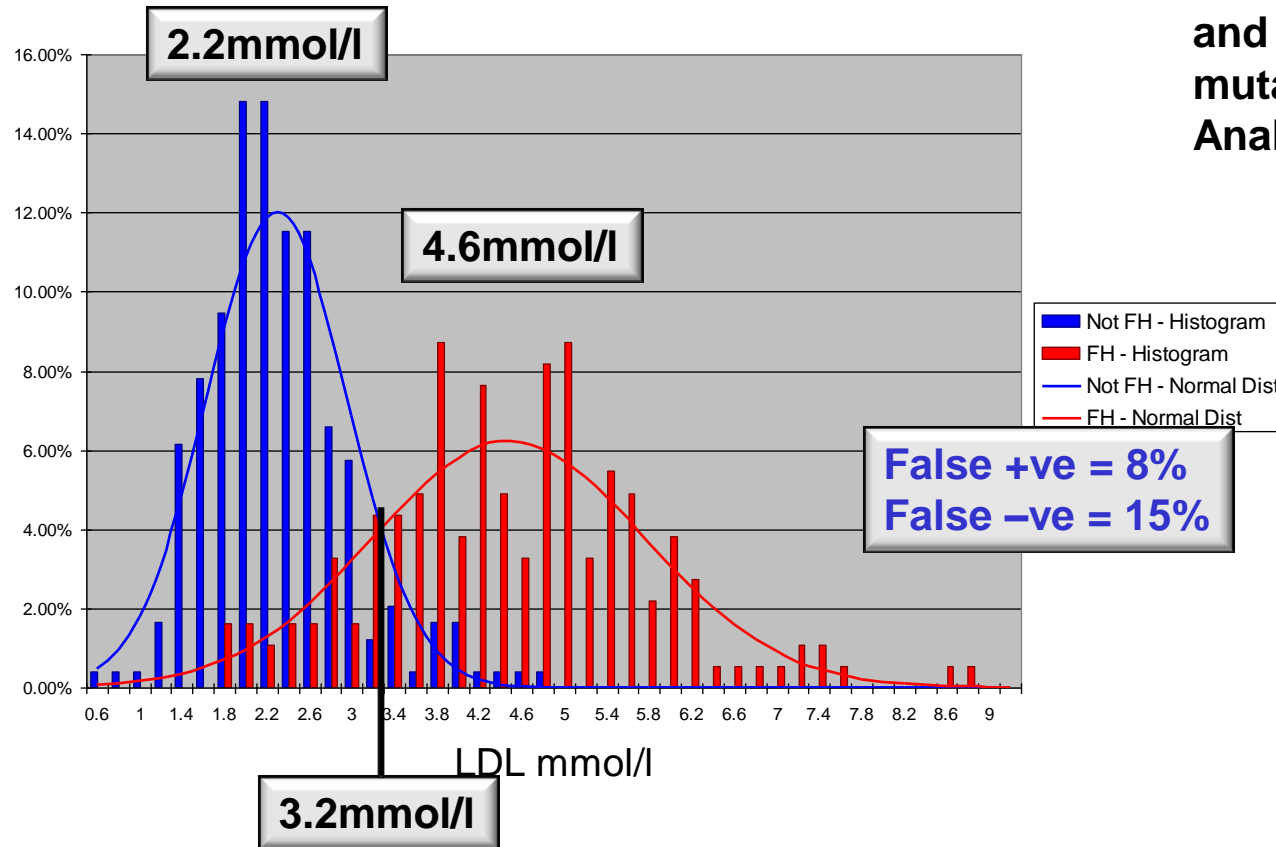
Why not just measure LDL-C?

The Overlap Problem

Data from Starr et al 2008

Collaboration with John Kastelein et al Amsterdam

FH vs. Not FH LDL levels, Ages 5-15



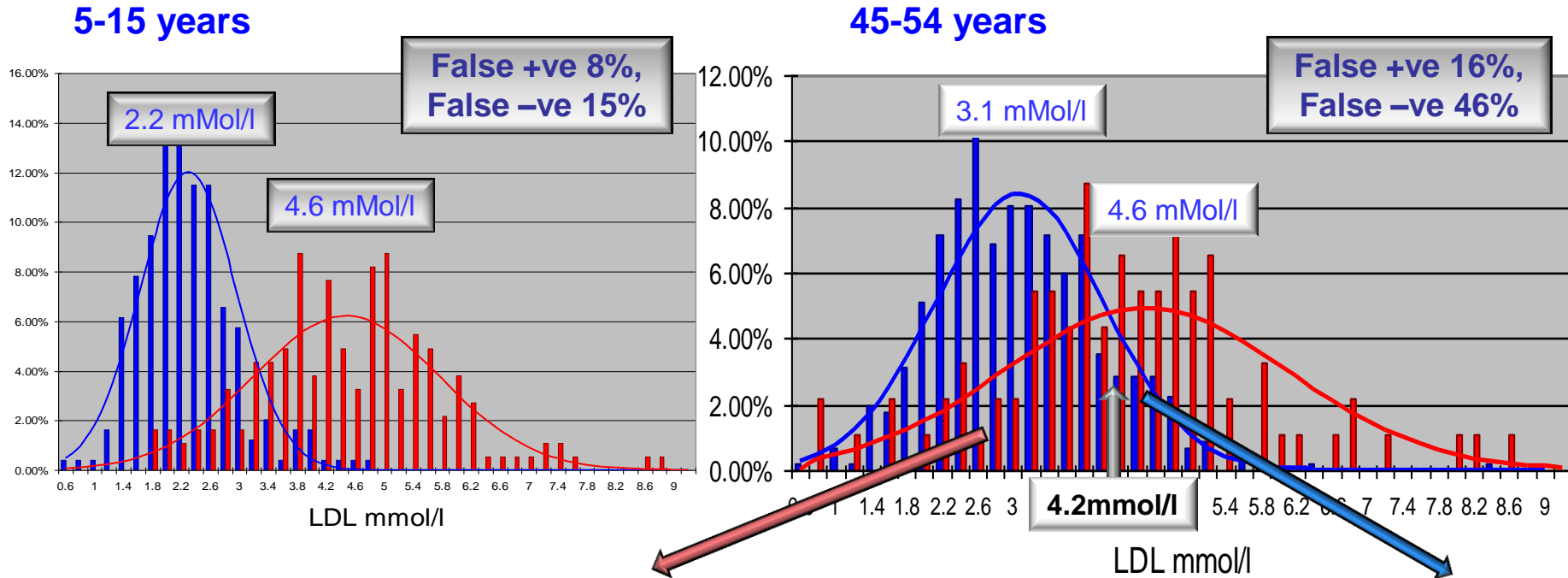
Data on 2469 non-carriers and 825 carriers of family mutation.
Analyse by age

Gets worse with age!

Using only LDL, ~15% FH children told they don't have FH!
DNA test avoids false -ve diagnosis

DNA testing for identification of relatives

As mean LDL-C rises with age in non-FH, overlap increases.



Below cut-off ~half of FH brothers and sisters of index case will not be tested

Above cut-off 16% of those tested will not have an FH-causing mutation

DNA testing gives an unambiguous result

Cascade testing needs Nurses – BHF funding

Used best available “real-life” UK data to estimate costs and benefits :

Costs

- Clinic Appointment
- Nurse time
- DNA/lipid tests,
- Statin/Ezetimibe treatment
- Annual Review
- Take up rate for tests
- Mutation detection rate
- Number of relatives contactable
- Current and future drug costs (off patent)

Benefits

- CVD events avoided
- Event rate in not-treated
- Achieved LDL-C reduction
- Estimated CVD reduction
- Costs of post event hospital & rehab
- Future Heart Failure avoided

The model consists of:

- Base case is no DNA tests, no cascade testing, no treatment of relatives
- For each strategy we calculate the cost per Quality-Adjusted Life-Years Gained (QALY)
- Key metric is Incremental Cost Effectiveness Ratio (ICER)

When comparing two strategies, the ICER is the increase in cost divided by the improvement in QALY.

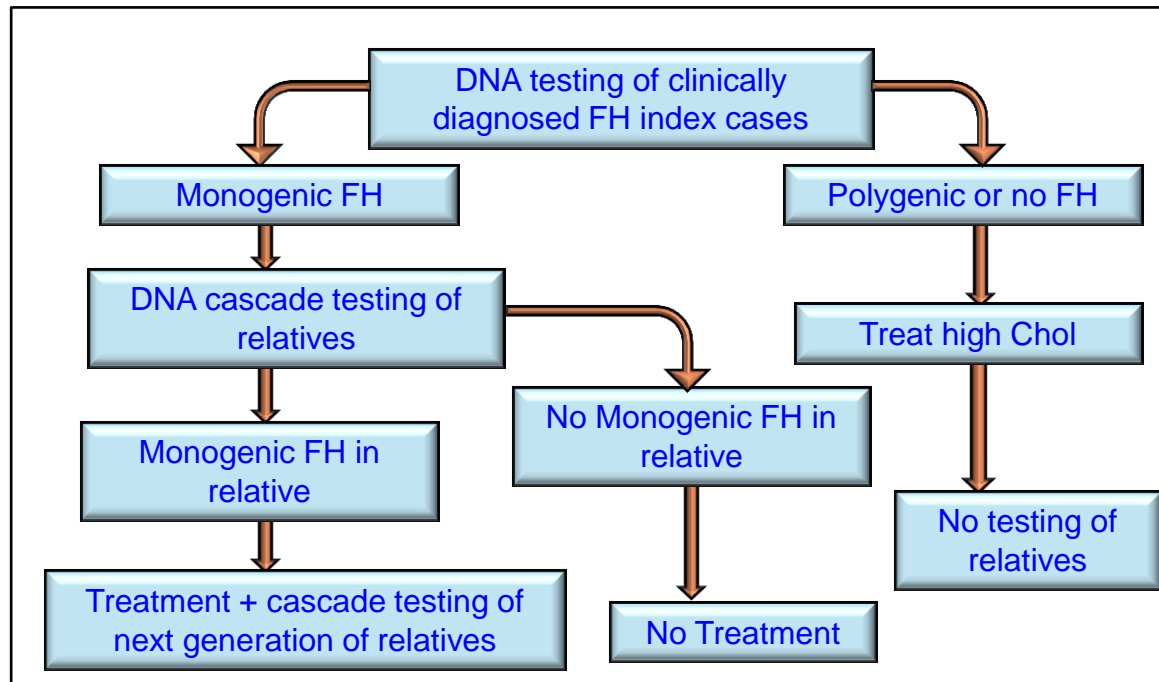
The model consisted of:

Kerr et al 2017

Decision tree to represent

- DNA testing of clinical FH index cases
- Identification of ONLY those with a monogenic cause
- Cascade testing of their relatives.
- Treatment decisions for relatives

High intensity statins+ezetimibe for mutation +ve relatives



Used Markov modelling to estimate benefits to relatives accrued over time

Does not include costs of finding index cases or their treatment

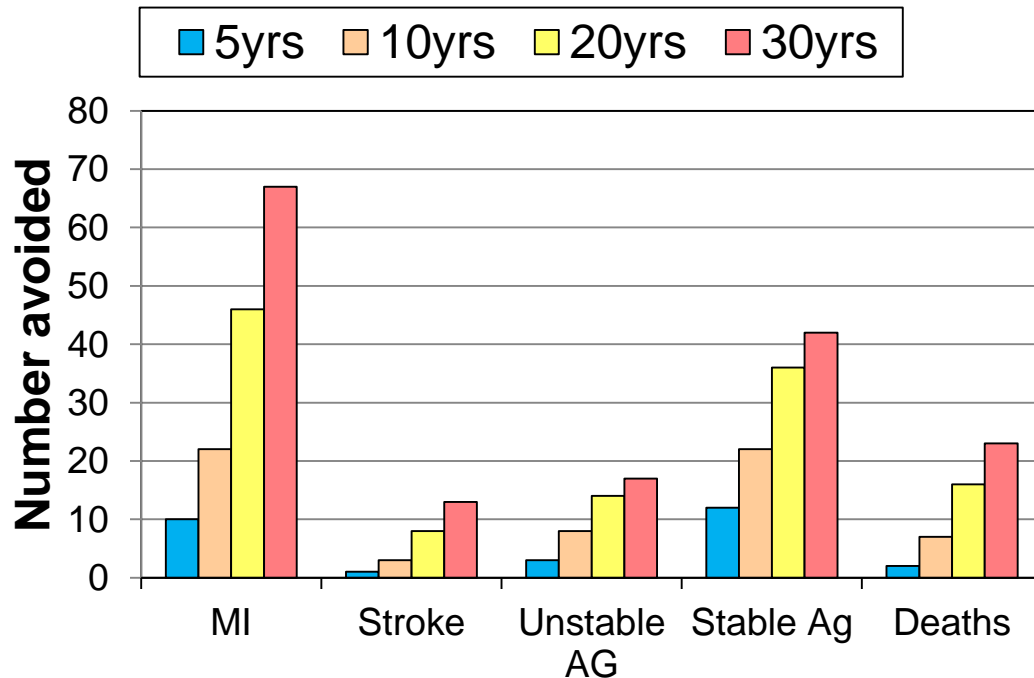
- Since Wales/Scotland and Wessex services established 6396 clinical FH index cases have had a DNA test.
- Of these **23%** have carried an FH-causing mutation.
- On average **1.33** relatives have been tested/monogenic index case
- In NI **6.8** relatives tested per monogenic index case
- Mean LDL-C in FH relatives = **6.67mmol/l**
- Assumed statin → reduction in LDL-C by **37%** (UK 2010 audit)
- Modelled potential reduction in CVD from CTTC estimates of benefit in general pop (may be > benefit in FH).

Predicts average **44%** reduction in CHD mortality, **60%** reduction in MI

A Reminder : When comparing two strategies, the Incremental Cost Effectiveness Ratio (ICER) is increase in cost divided by the improvement in QALY.

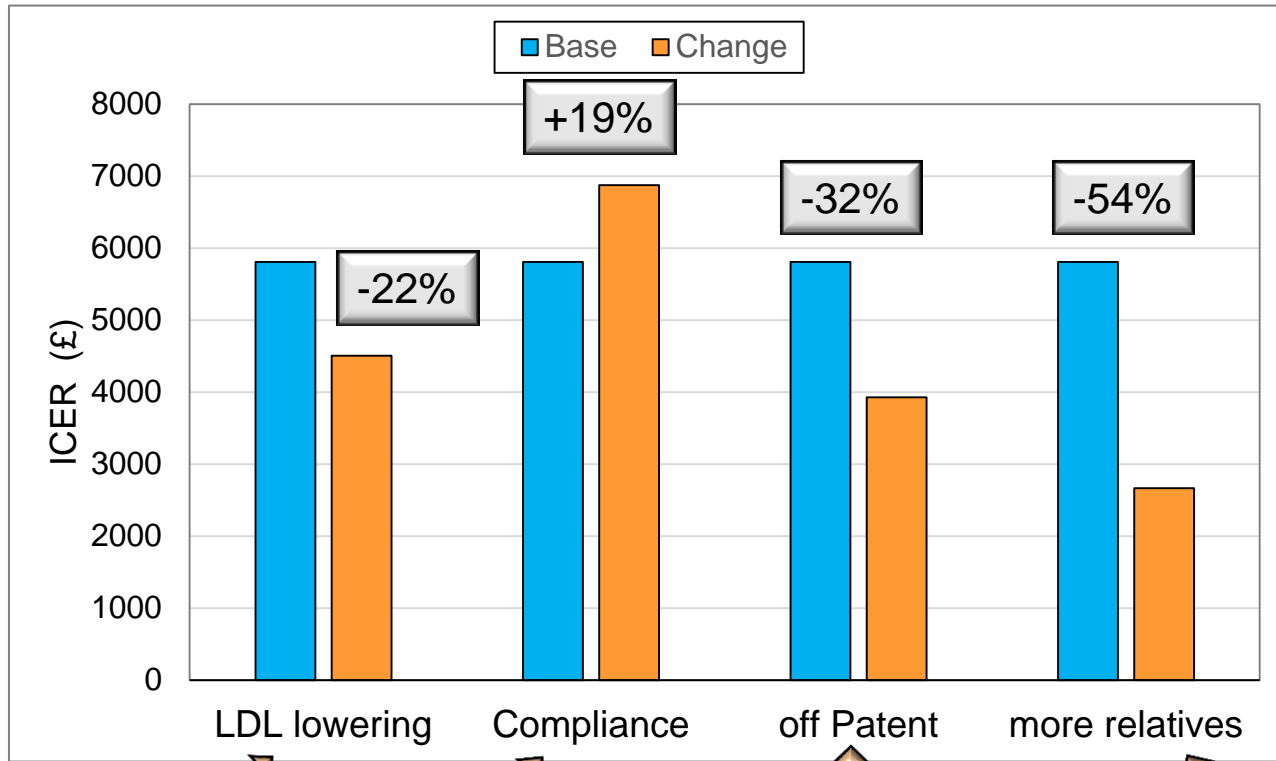
- Compared to no CT, the estimated ICER = £5,806
- This is considerably below threshold of £20,000 used in NHS

Estimated adverse events averted /1000 relatives tested



For every 1,000 relatives tested, over 30 years, 64 MIs, 57 cases of angina, 15 strokes and 23 deaths are averted at a cost of £2.8million

How could we improve the ICER?



Improve mean reduction in LDL-C 37% → 50%

Reduce statin compliance 100% → 70%

Reduce cost rosuvastatin and ezetimibe, after patent expiry

Increase the number of relatives tested/proband to that seen in NI

ICER is highly sensitive to the ratio of relatives tested per index case

Cascade testing of relatives of those with monogenic FH is highly cost effective

- >80% of costs were due to diagnosis costs incurred in the first year

DNA testing costs may soon be covered by NHS England

- Increasing the number of relatives tested per monogenic index case would significantly increase cost effectiveness.
- The current incompleteness of UK cascade services impacts testing rates for existing services – will improve over time.

Funding needed for Nation-wide coverage of FH Nurses

- If price Rosuvastatin → same as Atorvastatin and Ezetimibe to fall by 90%, the lifetime cost of cascade testing would fall by a third.

The systematic adoption of cascade testing services will yield substantial quality of life and survival gains

What is needed to carry out cascade testing efficiently?

- Guidelines with clear recommendations and patient care pathways
- A network of lipid clinics where GPs can refer patients
- FH Nurses to take detailed pedigrees, consent, blood for DNA tests, and contact details of relatives
- Accredited DNA testing laboratory (s) (ideally x2 in case one burns down!), offering NGS of all known FH-causing genes plus 12 SNP for polygenic score
- Paediatric services for identified children



All need clear funding stream for tests and treatment!

Costs used in Model

Test/Treatment/Adverse event	Annual/event cost/person (Range)
Genetic testing index cases	£352.50 (£255-£450)
Genetic testing in relatives	£119.78 (£65-£175),
Atorvastatin	£19.93
Simvastatin	£12.16
Rosuvastatin	£315.95 (£19.93 Sensitivity)
Fluvastatin	£37.32
Pravastatin	£15.08
Ezetimibe -40% FH	£342.97 (£34.30 Sensitivity)
Statin monitoring year 1	£120.17
Statin monitoring subsequent years	£100.71
Stable angina	£7,736.00
Post-stable angina	£240.00
Unstable angina	£3,313.00
Post-unstable angina	£385.00
MI	£3,731.00
Post-MI	£788.00
TIA	£640.00
Post-TIA	£124.00
Type 2 diabetes	£314.33
Stroke	£13,696.90
Post-stroke	£3,301.01

NICE 2017 update → recommendations for GPs

- Suspect familial hypercholesterolaemia (FH) as a possible diagnosis in adults with:
 - a total cholesterol level greater than 7.5 mmol/l **and/or**
 - a personal or family history of premature CHD (<60 years in an index individual or first-degree relative)
- Systematically search primary care records for those at high risk of FH:
 - <30 years, with a T-Cholesterol concentration > 7.5 mmol/l *
 - >30 years, with T-cholesterol concentration > 9.0 mmol/l*
- Refer the person to an FH specialist service for DNA testing if they meet the Simon Broome criteria for possible or definite FH, or they have a Dutch Lipid Clinic Network score greater than 5.

* = 99.5th %ile of UK population, ~28% will carry mutation - Futema et al 2013

Compared with cascade testing alone strategy had an
ICER of £1,572