Probabilistic cost-effectiveness analysis of cascade screening for Familial Hypercholesterolaemia using alternative diagnostic and identification strategies

Nherera L[1], Marks D[2], Minhas R[3], Thorogood M[4], Humphries SE [5]

[1] Health Economist, BMJ-Technology Assessment Group, BMJ Evidence Centre, BMJ Group. Tavistock Square, London. WC1H 9JR

[2] Department of Social & Environmental Health Research, London School of Hygiene & Tropical Medicine, Keppel Street, London WC1E 7HT

[3]Clinical Director, BMJ Evidence Centre, BMJ Group. Tavistock Square, London. WC1H 9JR

[4]Warwick Medical School, University of Warwick, Coventry CV4 7 AL

[5]Centre for Cardiovascular Genetics, British Heart Foundation Laboratories, Royal Free and University College London Medical School, 5 University Street, WC1E 6JJ

Address for correspondence:
Steve Humphries, Professor of Cardiovascular Genetics,
Centre for Cardiovascular Genetics, British Heart Foundation Laboratories,
Royal Free and University College London Medicine School,
3rd Floor, The Rayne Building,
5 University Street,
London WC1E 6JF, UK
Tel: +44 (0)20 679 6962
Fax: =44 (0)20 679 6212
rmhaseh@ucl.ac.uk

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Abstract

Objectives. To estimate the probabilistic cost-effectiveness ~~analysis~~ of cascade screening methods in people suspected of Familial Hypercholesterolaemia (FH) from the UK National ~~health~~ Health ~~service~~ Service perspective.

Design. Economic evaluation (Cost Utility analysis) comparing four cascade screening strategies for FH: 1. Using LDL-C measurements to diagnose affected relatives (Cholesterol method); 2. Cascading only in patients with a causative mutation identified and using DNA tests to diagnose relatives (DNA method); 3. DNA testing combined with LDL-C testing in families with no mutation identified, only in patients with clinically defined "Definite" FH (DNA+DFH method); 4. DNA testing combined with LDL-C testing in no-mutation families of both "Definite" and "Probable" FH patients (DNA+DFH+PFH). A probabilistic model was constructed to estimate the treatment benefit from statins, with all diagnosed individuals receiving high intensity statin treatment.

Setting. United Kingdom

Population. A cohort of 1000 people suspected of having FH aged 50 years for index cases and 30 years for relatives, followed for a lifetime.

Main outcomes. Costs, quality adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICERs)

Results. The DNA+DFH+PFH method was the most cost-effective cascade screening strategy. The ICER was estimated at £3,666/QALY. Using this strategy, of the tested relatives 30.6% will be true positives, 6.3% false positives, 61.9% true negatives and 1.1% false negatives. Probabilistic sensitivity analysis showed that this approach is 100% cost-effective using the conventional benchmark for cost-effective treatments in the NHS of between £20,000 and £30,000 per QALY gained.

Conclusion. Cascade testing of relatives of patients with DFH and PFH is cost-effective when using a combination of DNA testing for known family mutations and LDL-C levels in the remaining families. The approach is more cost-effective than current primary prevention screening strategies.

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Introduction

Familial hypercholesterolemia (FH) is characterized by hypercholesterolemia, xanthomas, and premature coronary heart disease (CHD) and affects around 1 in 500 people in western countries [1, 2]. It is a monogenic disorder caused by mutations in three genes: those coding for the receptor for low density lipoprotein (LDL) particles (*LDLR*), for apolipoprotein B (*APOB*) and for an enzyme involved in the degradation of the receptor as it recycles, *PCSK9*[3]. Treatment with statins is effective and reduces mortality[4,5]. In the UK less than 15% of the predicted 110,000 affected people are diagnosed[6].

FH is diagnosed in the UK using the Simon Broome Criteria[2,7] based on cholesterol levels (typically the ninety-fifth percentile of total serum cholesterol or LDL-cholesterol (LDL-C) is a cut-off value), family history of hyperlipidaemia or early CHD, and presence of (or family history of) xanthomas. Individuals fulfilling these criteria, and those found to carry an FH-causing mutation are given the diagnosis of definite FH (DFH), while those showing only elevated cholesterol levels together with a family history of hyperlipidaemia or early CHD are given the diagnosis of possible FH (PFH).

There is considerable overlap in the distribution of LDL-C levels between individuals with and without FH. In children, where the overlap is least[8,9], using a simple cut off results in a false positive rate of 8-10% and a false negative rate of 10-15%. In adults, the false negative is greater[10]. Also, an individual's cholesterol levels may fluctuate, moving from below to above the cut-off value on repeat measurements. Thus, some patients will be given a false negative diagnosis (i.e. told that they do not have FH when they do), while others will be given a false positive diagnosis (told that they have FH when they do not).

When DNA testing is used to diagnose FH, a mutation can be identified in 60-90% of DFH patients[11, 12], depending on the sensitivity of the methods and the population under consideration. By comparison, a mutation can be identified in only 20-30% of PFH patients[13]. Once the underlying mutation has been identified, molecular genetic screening of first degree relatives has a sensitivity and specificity close to 100%.

The UK National Institute for Health and Clinical Excellence (NICE) has recommended, based on deterministic economic evaluation of the alternative approaches to cascade screening[14,15] the use of "cascade screening" of first degree relatives of patients with FH using cholesterol measurement and DNA methods in combination. This paper presents the results of a probabilistic economic analysis to compare the costs and benefits of alternative screening strategies in terms of quality adjusted life years (QALYs).

Methods

Model structure, assumptions and analytical methods

We constructed a decision tree in Excel™ where a hypothetical 1000 patients referred from general practice with a suspicion of heterozygous FH entered the model. Figure 1 shows a schematic presentation of the decision problem and a full breakdown of the decision pathways. The decision pathways for all the methods under consideration each have three disease states which depict the initial diagnosis i.e. definite FH, possible FH and not FH, as defined by the Simon Broome[7] and the FHCAP study[16]. Subsequent branches of the tree are dependent on the cascade screening method under consideration which are described in detail below. Once individuals are identified as true positives (TP), false positives (FP), true negatives (TN) and false negatives (FN) at the end of the decision tree, they enter into a Markov model according to the treatment protocol also described below. Four cascade screening methods were compared:

1. *The cholesterol method*: This is the standard method of clinical diagnosis and identification of affected relatives using elevation of LDL-C levels. Only patients meeting the criteria of DFH or PFH were included for cascade testing.

2. *The DNA* method*:* The identification of an FH-causing mutation by molecular genetics methods, firstly in the index patient and then in first degree relatives. Only patients with an identified FH-causing mutation were included for cascade testing.

3. *The DNA+DFH* method: Following DNA testing of the index cases cascade testing of relatives is undertaken in all mutation-positive index cases but additionally, in the relatives of DFH index cases where no mutation can be found, cascade testing is undertaken using cholesterol (LDL-C) levels to identify affected relatives

4. *The DNA+DFH+PFH* method: Following DNA testing of the index cases cascade testing of relatives is undertaken in all mutation-positive index cases but additionally, in the relatives of DFH and PFH index cases where no mutation can be found, cascade testing is undertaken using cholesterol (LDL-C) levels to identify affected relatives.

Treatment protocol and estimated long-term benefits from statin treatment.

All index cases and relatives with a diagnosis of FH (whether DFH or PFH) are assumed to be offered high intensity statin therapy, in line with NICE guideline on FH[14], while true and false negatives were assumed to be on low intensity statin. For the relatives, a proportion (1.3%) [30]

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[17] of the subjects with either a true negative or a false negative diagnosis will require treatment with low intensity statins, because the combination of their lipid and other cardiovascular risk factors brings their 10 year CVD risk to >20% . False positives were given high intensity statin but did not benefit from the statin, rather they incurred a disutility (reduction in quality of life) estimated to be about 3% and then varied in sensitivity analysis (Expert opinion). We developed a Markov model using Microsoft™ Excel to estimate the treatment benefit from statins. The structure of the model is described in detail previously [~~18~~18], and used data from the Simon Broome Study [7, ~~19~~19]. Death from other causes was assumed to be the same as that of the general population and was taken from the life tables of the England and Wales Government Actuary Department (2006)[20]. The model assumes that risk of cardiovascular disease (CVD) increases with age for both males and females~~.~~[~~20~~1]. The risk of stroke and peripheral artery disease were assumed to be the same as seen in the general population, because data from the Simon Broome Register indicated that these risks are not significantly higher in the FH population[22] Treatment effects of statins were taken from a meta-analysis of the four trials that compared high intensity statins with low intensity statins after myocardial infarction – see T~~t~~able 3[~~21~~3,~~24~~2,~~23~~,~~24~~5,26].

Comment [p2]: Does it matter that table 3 is mentioned before table 1 & 2?

Cost data

Drug costs were taken from the ~~BNF~~[~~25~~]-BNF [27] (number ~~59~~61, ~~2010~~2011) and are shown in supplementary ~~table~~ Table 5. Costs of full fasting and non-fasting cholesterol measurements and costs of CVD events were taken from NHS reference ~~costs~~[~~26~~]costs[28,~~27~~29]. All costs were at ~~2009~~ 2010/11 prices and as per current NICE guidance; an annual discount rate of 3.5% was used for both costs and health benefits.

Outcomes and quality of life (Utility)~~:~~

Clinical outcomes modelled were myocardial infarction, stroke, heart failure, transient ischaemic attack; peripheral arterial disease, unstable angina, revascularisation, cardio-vascular and total mortality. Utility weights for the various health states and age adjusted utility from were taken from our earlier study [~~18~~18]. Age adjusted utility was solicited from the general population using time trade off [~~30~~-30] (see supplementary ~~table~~ Table 2 and 3). The beneficial value of health outcomes was estimated using the Quality Adjusted Life Year (QALY). We did not allow for any harmful effects of treatment with statins since significant side-effects are relatively uncommon ~~especially in high risk populations~~[31~~28~~] but assessed their impact in sensitivity analysis.

Probabilistic sensitivity analysis

Due to imperfect information on the effectiveness of intervention and the resources consumed for treatment, both the costs and effects of health interventions are inevitably associated with some degree of uncertainty, and this introduces the possibility of error into decision-making [29][32]. In our analysis we used Monte Carlo simulation to generate the sampling distribution of the joint mean cost and efficacy in order to quantify the uncertainty around the estimates of costs and effects. In addition we ~~also~~ did one-way sensitivity analysis on variables which had uncertain estimates and yet were likely to influence overall conclusions. These included the cost of the cholesterol method, a reduction in the cost of statins, any potential loss in quality of life due to side effects of high dose statins and the costs of DNA testing.

Results

The four cascade screening methods identified differing numbers of true and false negatives and positives amongst both cases and relatives (Table 1). The DNA only strategy required the least number of relatives to be tested, but did not identify as many true positives as the DNA+DFH+PFH strategy. This last strategy was also the strategy that required the largest number of relatives to be screened.

Costs of diagnosis and treatment

Table 2 shows the cost of diagnosis and treatment of people diagnosed with either monogenic or polygenic hypercholesterolaemia for each of the four strategies, using the treatment protocol outlined above in the methods section, while Table 3 shows the QALYs gained in each strategy. The total costs of diagnosis for the index case included the total cost of clinical confirmation for index cases (lipid profile + health care professional costs, estimated to be £240 per index case and £139 per relative) and the cost of DNA testing. The cost per relative included the costs of sending out letters. These costs were multiplied by the numbers of people tested under each strategy. DNA testing and cascading was not done in those 100 individuals identified in each strategy as true negatives.

The cost of treatment and QALY gain per individual was estimated from the Markov model for each strategy under consideration. The number of index and relative cases identified by each strategy was multiplied by the cost and QALY gain per individual. Thus the total cost of each strategy was the sum of the diagnosis and treatment costs.

Cost effectiveness

As shown in Table 4, all DNA based methods were cost-effective relative to the cholesterol only method. However, cascade testing from DNA+DFH is ruled out by extended dominance. The principle of extended dominance is applied in incremental cost-effectiveness analyses to eliminate from consideration strategies whose costs and benefits are improved by a mixed strategy of two other ~~alternatives~~[31] alternatives[33]. Thus the combinations of DNA only and DNA+DFH+PFH are both more cost-effective than DNA+DFH. After accounting for the options ruled out by extended dominance, the relevant incremental comparison is between the DNA method and the DNA+DFH+PFH method. The estimated base case incremental cost-effectiveness ratio (ICER) is £3,666/QALY, as shown in Table 4.

We assessed uncertainty around this ICER by Monte-Carlo simulation using 2000 iterations. Figure 2 illustrates the probability that any one strategy is cost-effective, as a function of the willingness to pay. Given a maximum acceptable ceiling ratio of £20,000/QALY the probability that DNA+DFH+PFH is cost-effective compared to the DNA method is 100%. Thus, given the data, there is a 100% chance that the additional cost of DNA+DFH+PFH, compared with the DNA method, is at or below £20,000 per QALY gained.

One way sensitivity analysis showed that the model results were not sensitive to changes in assumptions about loss in quality of life due to side effects of high dose statins as the ICERs remained below £20,000/QALY when the assumption was varied between 1% and 10%.

We also varied the cost of statins as we expect atorvastatin to be off patent in 2011. We thus reduced the cost of atorvastatin by 60% and the cost-effectiveness results became more favorable with the ICER falling from the current estimate of £3,666 to £3,070/QALY. We also varied other variables like the proportions of index cases and relatives who agreed to testing, the age at identification for index cases and relatives, and the cost of cholesterol testing and DNA costs, and in all cases the ICERs remained below £4,000/QALY, suggesting the model is not sensitive to changes in these parameters. The base model assumed that there was no quality of life loss associated with side effects of statins, and when we assumed a 5% loss in quality of life the ICER increased only slightly to £4,028 demonstrating that the model results are also not sensitive to this assumption.

Discussion

Our economic analysis indicates that the most cost-effective cascade screening strategy for people suspected of Familial Hypercholesterolaemia is DNA testing plus cascading from both mutation negative definite and possible FH individuals, with an estimated ICER of

£3,666/QALY when compared to the DNA only method. Our results were stable in univariate sensitivity analysis. Probabilistic sensitivity analysis also showed that the DNA+DFH+PFH strategy is 100% cost-effective as it falls below the recommended £20,000/QALY threshold currently used in the UK for evaluating interventions. Altering assumptions about several key determinants of cost and effectiveness including the cost of statins (which will fall in the near future as some of the potent statins recommended for FH patients come off-patent), the cost of DNA testing, the overall cost of the cholesterol measures, the proportions of index cases and relatives who agreed to testing, and the age at identification for index cases and relatives did not materially influence the ICERs. There is no uncertainty that DNA+DFH +PFH is the most cost-effective option.

Strengths and weaknesses

To our knowledge this is the first probabilistic analysis of FH screening strategies for the UK.

Because patients with FH have very high LDL-C levels from birth, they will frequently require high intensity lipid lowering therapy sufficient to reduce LDL-C to recommended levels[14,15] and studies have shown that statin treatment reduces their premature mortality[5]. In our model we have used a combination of statins but the model was not sensitive to different combinations of statins. We have assumed that any individual identified with elevated LDL cholesterol levels will be treated whether or not they carried the family mutation. Individuals who do not carry the mutation are likely to be treated with a lower dose of statin and the costs and benefits for this have been included in the model. The results of our model were not sensitive to the documented side effects of statins[~~32~~ 34,35] since variations in screening methods influence numbers of people allocated to high or low dose, but have no influence on the QALY gain from the statin treatment.

Because observational data from the Simon Broome Register cohort showed no significant increase in mortality in FH patients over 60 years old[4], we have assumed that people over the age of 60 will benefit from statins to the same degree as the general population. This does not support ceasing treatment at age 60 in people diagnosed with FH. People with FH who have reached this age or beyond without treatment and without experiencing any cardiovascular event or symptoms appear to have a risk low enough not to warrant high intensity treatment, that is, a survivor effect.

Our model did not consider cascade testing from children due to a lack of data on the effectiveness of statins in children. If children were included in the case-finding approach, this strategy is likely to become even more cost-effective as the number of relatives per index

case would increase. A false-negative diagnosis may deny both the patient who has FH and that person's relatives with FH the benefit of more intensive cholesterol lowering therapy. By contrast, cascade screening from false-positive cases will not identify any true FH patients and will waste resources. It would be possible to reduce the numbers of false positives and negatives if better data were available on the range of LDL-C levels to be expected in the mutation carrying relatives of patients with FH, and the extent to which this range overlaps with that in non-mutation carrying relatives.

Markov models have inherent limitations. They assume that the probability of an individual moving to any given health state in one time period depends only on their current health state (there is no longer 'memory' in the model). Similarly, a patient's health outcome and health care costs incurred are assumed to depend only on their current health state. These assumptions are unlikely to be strictly true, and will tend to underestimate the costs and overestimate the health outcomes for CVD events. Thus, interventions that prevent more CVD events will appear less cost-effective than they may be in reality.

Comparison with other studies

Our findings that DNA based screening methods are more cost-effective are consistent with other published studies. Marks et ~~al~~[33] al[36] undertook a cost-effectiveness analysis from the NHS perspective. These included universal screening, opportunistic screening in primary care, screening of people admitted to hospital with premature myocardial infarction, or tracing family members of affected patients. They concluded that screening family members was the most cost-effective strategy, with an estimated ICER of £3097 per life year gained (LYG) using cholesterol measurement for diagnosis and £4914/LYG using DNA testing, while universal population screening using cholesterol measurement only was a much less cost-effective strategy with an estimated ICER of £13,029/LYG. Marks et ~~al~~[34] al[37] also considered the costs and deaths averted over 10 years from either a population strategy of screening 16 year olds or tracing family members of affected patients. They concluded that family tracing was again the most efficient strategy, with the cost per death averted being £3187. A cost-effectiveness study of the FH genetic screening programme in the Netherlands resulted in a similar cost per life-year gained of US$ 8, 800 [35]~~38~~. The result was sensitive to the price of statin treatment and the number of life-years gained.

Our results also compares favorably with strategies to identify individuals at a lower risk of cardiovascular disease (i.e. primary prevention), which were evaluated in a previous NICE guideline in which the recommended screening strategy (targeted screening) has an ICER of £7604/~~QALY~~[36] QALY[39].

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Implications and future research

There is a lack of UK data describing the range of LDL-C levels to be expected in the mutation carrying relatives of patients with FH, and the extent to which this range overlaps with that in non-mutation carrying relatives. Further research is required to characterise the distributions of LDL-C levels in mutation-carrying relatives of patients with FH and the extent of overlap with levels in other relatives to improve the performance of screening strategies. The cost-effectiveness of DNA screening is likely to improve in the future as the proportion of definite FH patients in whom a mutation can be identified increases because of improvements in techniques for mutation identification, and also because of the identification of new genes where mutations cause FH. However, even now this economic analysis supports the identification and treatment of individuals with FH as a highly cost-effective strategy in the prevention of cardiovascular disease.

Conclusion

National strategies to reduce the burden of cardiovascular disease in the UK would be made more effective and more cost effective by incorporating the screening strategy that was recommended in national guidance from NICE for the identification and treatment of people with Familial Hypercholesterolemia. To date we are not aware that there has been any local implementation of such a strategy in England.

Conflicts of Interest:

LN, RM, MT and SH were members of the Guideline Development Group for the Guideline for identification and management of adults and children with familial hypercholesterolaemia. DM has no conflicts to declare. Any opinions expressed in this paper are those of the authors and not intended to represent those of any affiliated organisations.

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WHAT IS ALREADY KNOWN ON THIS TOPIC

Familial Hypercholesterolaemia is a common genetic disorder where patients have a very high risk of early onset heart disease that can be effectively treated with high intensity statins. Currently in the UK, less than 15% of the predicted 110,000 patients are diagnosed and there are no commissioned services to identify people with this condition. Clinical and cost effective strategies for the identification of patients with this condition and their implementation are urgently required.

WHAT THIS STUDY ADDS

Cascade testing from index patients with both clinically defined definite and possible FH is highly cost-effective when using a combination of DNA testing for the family mutation where it can be found and LDL-C levels where it cannot. Cascade testing to identify relatives of patients with FH is also more cost effective than recently recommended primary prevention screening strategies. The approach will become even more cost-effective as technological advances reduce the cost of DNA testing and increase its sensitivity and following the patent expiry of high intensity statins.

References

1. Austin MA, Hutter CM, Zimmern RL et al. Genetic causes of monogenic heterozygous familial hypercholesterolemia: a HuGE prevalence review. Am J Epidemiol 2004; 160:407-420.

2. Marks D, Thorogood M, Neil HA et al. A review on the diagnosis, natural history, and treatment of familial hypercholesterolaemia. Atherosclerosis 2003;168:1-14.

3. Varret M, Abifadel M, Rabes JP, Boileau C: Genetic heterogeneity of autosomal dominant hypercholesterolemia. Clin Genet 2008; 73:1-13.

4. Betteridge D. Mortality in treated heterozygous familial hypercholesterolaemia: implications for clinical management. Athereosclerosis 1999; 142:105-112.

5. Neil A, Cooper J, Betteridge J et al. Reductions in all-cause, cancer, and coronary mortality in statin-treated patients with heterozygous familial hypercholesterolaemia: a prospective registry study. Eur Heart J 2008; 29:2625-33.

6. Marks D, Thorogood M, Farrer JM, Humphries SE. Census of clinics providing specialist lipid services in the United Kingdom. J Public Health 2004; 26:353-354.

7. The Simon Broome Register Group. Scientific Steering Committee on behalf of The Simon Broome Register Group. The risk of fatal coronary heart disease in familial hypercholesterolaemia. BMJ 1991; 303:893-896.

8. Kwiterovich PO Jrn, Fredrickson DS, Levy RI. Familial hypercholesterolemia (one form of familial type II hyperlipoproteinemia). A study of its biochemical, genetic and clinical presentation in childhood. Journal of Clinical Invest 1974; 53:1237-1249.

9. Leonard JV, Whitelaw AG, Wolff OH et al. Diagnosing familial hypercholesterolaemia in childhood by measuring serum cholesterol. Br Med J. 1977; 18; 1:1566-8.

10. Starr B, Hadfield SG, Hutten BA, et al. Development of sensitive and specific age- and gender-specific low-density lipoprotein cholesterol cut-offs for diagnosis of first-degree relatives with familial hypercholesterolaemia in cascade testing. Clin Chem and Lab 2008; 46:791-803.

11. Graham CA, McIlhatton BP, Kirk CW et al. Genetic screening protocol for familial hypercholesterolemia which includes splicing defects gives an improved mutation detection rate. Atherosclerosis 2005; 182:331-340.

12. Humphries SE, Whittall RA, Hubbart CS et al. Genetic causes of familial hypercholesterolaemia in patients in the UK: relation to plasma lipid levels and coronary heart disease risk. J Med Genet 2006; 43:943-949.

13. Taylor A, Wang D, Patel et al. Mutation detection rate and spectrum in familial hypercholesterolaemia patients in the UK pilot cascade project. Clin Genet 2010; 77:572-580.

14. DeMott K, Nherera L, Shaw EJ et al. Clinical Guidelines and Evidence Review for Familial hypercholesterolaemia: the identification and management of adults and children with familial hypercholesterolaemia. 2008. London: National Collaborating Centre for Primary Care and Royal College of General Practitioners.

15. Minhas R, Humphries SE, Qureshi N, Neil HA; NICE Guideline Development Group. Controversies in familial hypercholesterolaemia: recommendations of the NICE Guideline Development Group for the identification and management of familial hypercholesterolaemia. Heart. 2009 Apr;95(7):584-7

16. Hadfield SG, Horara S, Starr BJ et al. Steering Group for the Department of Health Familial Hypercholesterolaemia Cascade Testing Audit Project. Family tracing to identify patients with familial hypercholesterolaemia: the second audit of the Department of Health Familial Hypercholesterolaemia Cascade Testing Project. Ann Clin Biochem.2009; 46:24-32.

17. Health Survey of England 2003 http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsStatistics/DH_4098712

18. Nherera L, Calvert NW, DeMott K et al. Cost-effectiveness analysis of the use of a high-intensity statin compared to a low-intensity statin in the management of patients with familial hypercholesterolaemia. Curr Med Res Opin 2010; 26:529–36.

19. Hadfield SG, Horara S, Starr BJ et al. Steering Group for the Department of Health Familial Hypercholesterolaemia Cascade Testing Audit Project. Family tracing to identify patients with familial hypercholesterolaemia: the second audit of the Department of Health Familial Hypercholesterolaemia Cascade Testing Project. Ann Clin Biochem.2009; 46:24-32.

20. Government Actuary's Department. Interim Life Tables: Governement Actuary's Department, 2006 http://www.gad.gov.uk/Demography_Data/Life_Tables/Interim_life_tables.asp

21. National Institute for Health and Clinical Excellence. Statins for the prevention of cardiovascular events. Technology Appraisal http://www.nice.org.uk/Guidance/TA94. London: National Institute for Health and Clinical Excellence, 2006.

22. Huxley RR, Hawkins MH, Humphries SE et al. Simon Broome Familial Hyperlipidaemia Register Group and Scientific Steering Committee. Risk of fatal stroke in patients with treated familial hypercholesterolemia: a prospective registry study. Stroke. 2003; 34:22-5.

23. LaRosa JC, Grundy SM, Waters DD et al. Intensive Lipid Lowering with Atorvastatin in Patients with Stable Coronary Disease. N Eng J Med 2005;352:1425-1435.

24. Pedersen TR, Faergeman O, Kastelein JJP et al. High-dose atorvastatin vs usual-sose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. JAMA 2005;294:2437-2445.

25. Cannon CP, Braunwald E, McCabe CH et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004;350:1495-504.

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26. de Lemos JA, Blazing MA, Wiviott SD et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes phase Z of the A to Z Trial. JAMA 2004;292:1307-16.

27. British National Formulary March 2011 Number 61. Available from http://bnf.org/bnf/index.htm

28. Curtis, L. & Netten, A. (2010) Unit Costs of Health and Social Care 2010, Personal Social Services Research

29. Department of Health, NHS reference costs 2010/11. Reference Costs 2010. Available http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_111591

30. Health survey of England 1996, Adjusting utility for age http://www.archive.official-documents.co.uk/document/doh/survey96/tab5-29.htm

31. Taylor F, Ward K, Moore THM, Burke M, Davey Smith G, Casas JP, Ebrahim S. Statins for the primary prevention of cardiovascular disease. Cochrane Database of Systematic Reviews 2011, Issue 1. Art. No.: CD004816. DOI: 10.1002/14651858.CD004816.pub4.

32. Fenwick, E, O'Brien, BJ, Briggs, A. Cost-effectiveness acceptability curves - facts, fallacies and frequently asked questions. Health Econ 2004;13:405-415.

33. Cantor S.B Medical.Cost - Effectiveness analysis, extended dominance, and ethics: a quantitative assessment. Med Decis Making. 1994; 14:259-65.

34. Hippisley-Cox J, Coupland C. Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database. BMJ. 2010 May 20; 340:c2197. doi: 10.1136/bmj.c2197

35. Hippisley-Cox J, Coupland C. Individualising the risks of statins in men and women in England and Wales: population-based cohort study.Heart. 2010 Jun;96(12):939-47.

36. Marks D, Wonderling D, Thorogood M et al. Cost-effectiveness analysis of different approaches of screening for familial hypercholesterolaemia. [See comment]. BMJ 2002; 324:1303-1306.

37. Marks D, Thorogood M, Neil HA, et al. Comparing costs and benefits over a 10 year period of strategies for familial hypercholesterolaemia screening. J Public Health Med 2003; 25:47-52.

38. Wonderling D, Umans-Eckenhausen MA, Marks D et al. Cost-effectiveness analysis of the genetic screening program for familial hypercholesterolemia in The Netherlands. Semin in Vasc Med 2004; 4:97-104.

39. National Institute for Health and Clinical Excellence. Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. 2008. http://guidance.nice.org.uk/CG67.

References

1. Austin MA, Hutter CM, Zimmern RL et al. Genetic causes of monogenic heterozygous familial hypercholesterolemia: a HuGE prevalence review. Am J Epidemiol 2004; 160:407-420.

2. Marks D, Thorogood M, Neil HA et al. A review on the diagnosis, natural history, and treatment of familial hypercholesterolaemia. Atherosclerosis 2003;168:1-14.

3. Varret M, Abifadel M, Rabes JP, Boileau C: Genetic heterogeneity of autosomal dominant hypercholesterolemia. Clin Genet 2008; 73:1-13.

4. Betteridge D. Mortality in treated heterozygous familial hypercholesterolaemia: implications for clinical management. Athereosclerosis 1999; 142:105-112.

5. Neil A, Cooper J, Betteridge J et al. Reductions in all-cause, cancer, and coronary mortality in statin-treated patients with heterozygous familial hypercholesterolaemia: a prospective registry study. Eur Heart J 2008; 29:2625-33.

6. Marks D, Thorogood M, Farrer JM, Humphries SE. Census of clinics providing specialist lipid services in the United Kingdom. J Public Health 2004; 26:353-354.

7. The Simon Broome Register Group. Scientific Steering Committee on behalf of The Simon Broome Register Group. The risk of fatal coronary heart disease in familial hypercholesterolaemia. BMJ 1991; 303:893-896.

8. Kwiterovich PO Jrn, Fredrickson DS, Levy RI. Familial hypercholesterolemia (one form of familial type II hyperlipoproteinemia). A study of its biochemical, genetic and clinical presentation in childhood. Journal of Clinical Invest 1974; 53:1237-1249.

9. Leonard JV, Whitelaw AG, Wolff OH et al. Diagnosing familial hypercholesterolaemia in childhood by measuring serum cholesterol. Br Med J. 1977; 18; 1:1566-8.

10. Starr B, Hadfield SG, Hutten BA, et al. Development of sensitive and specific age- and gender-specific low-density lipoprotein cholesterol cut-offs for diagnosis of first-degree relatives with familial hypercholesterolaemia in cascade testing. Clin Chem and Lab 2008; 46:791-803.

11. Graham CA, McIlhatton BP, Kirk CW et al. Genetic screening protocol for familial hypercholesterolemia which includes splicing defects gives an improved mutation detection rate. Atherosclerosis 2005; 182:331-340.

12. Humphries SE, Whittall RA, Hubbart CS et al. Genetic causes of familial hypercholesterolaemia in patients in the UK: relation to plasma lipid levels and coronary heart disease risk. J Med Genet 2006; 43:943-949.

13. Taylor A, Wang D, Patel et al. Mutation detection rate and spectrum in familial hypercholesterolaemia patients in the UK pilot cascade project. Clin Genet 2010; 77:572-580.

14. DeMott K, Nherera L, Shaw EJ et al. Clinical Guidelines and Evidence Review for Familial hypercholesterolaemia: the identification and management of adults and children with familial hypercholesterolaemia. 2008. London: National Collaborating Centre for Primary Care and Royal College of General Practitioners.

15. Wierzbicki AS, Humphries SE, Minhas R; Guideline Development Group. Familial hypercholesterolaemia: summary of NICE guidance. BMJ. 2008 Aug 27;337:a1095

16. Hadfield SG, Horara S, Starr BJ et al. Steering Group for the Department of Health Familial Hypercholesterolaemia Cascade Testing Audit Project. Family tracing to identify patients with familial hypercholesterolaemia: the second audit of the Department of Health Familial Hypercholesterolaemia Cascade Testing Project. Ann Clin Biochem.2009; 46:24-32.

17. Nherera L, Calvert NW, DeMott K et al. Cost-effectiveness analysis of the use of a high-intensity statin compared to a low-intensity statin in the management of patients with familial hypercholesterolaemia. Curr Med Res Opin 2010; 26:529-36.

18. Huxley RR, Hawkins MH, Humphries SE et al. Simon Broome Familial Hyperlipidaemia Register Group and Scientific Steering Committee. Risk of fatal stroke in patients with treated familial hypercholesterolemia: a prospective registry study. Stroke. 2003; 34:22-5.

19. National Institute for Health and Clinical Excellence. Statins for the prevention of cardiovascular events. Technology Appraisal http://www.nice.org.uk/Guidance/TA94. London: National Institute for Health and Clinical Excellence, 2006.

20. LaRosa JC, Grundy SM, Waters DD et al. Intensive Lipid Lowering with Atorvastatin in Patients with Stable Coronary Disease. N Eng J Med 2005;352:1425-1435.

21. Pedersen TR, Faergeman O, Kastelein JJP et al. High-dose atorvastatin vs usual-sose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. JAMA 2005;294:2437-2445.

22. Cannon CP, Braunwald E, McCabe CH et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004;350:1495-504.

23. de Lemos JA, Blazing MA, Wiviott SD et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes phase Z of the A to Z Trial. JAMA 2004;292:1307-16.

24. British National Formulary Sept 2009 Number 58. Available from http://bnf.org/bnf/index.htm

25. Curtis, L. & Netten, A. (2009) Unit Costs of Health and Social Care 2009, Personal Social Services Research

26. Department of Health, NHS reference costs 2008/9. Reference Costs 2008. Available http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_111591

27. Fenwick, E, O'Brien, BJ, Briggs, A. Cost-effectiveness acceptability curves - facts, fallacies and frequently asked questions. Health Econ 2004;13:405-415.

28. Health Survey of England 2003 http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsStatistics/DH_4098712

29. Cantor S.B Medical.Cost - Effectiveness analysis, extended dominance, and ethics: a quantitative assessment. Med Decis Making. 1994; 14:259-65.

30. Hippisley-Cox J, Coupland C. Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database. BMJ. 2010 May 20; 340:c2197. doi: 10.1136/bmj.c2197

31. Marks D, Wonderling D, Thorogood M et al. Cost effectiveness analysis of different approaches of screening for familial hypercholesterolaemia. [See comment]. BMJ 2002; 324:1303-1306.

32. Marks D, Thorogood M, Neil HA, et al. Comparing costs and benefits over a 10 year period of strategies for familial hypercholesterolaemia screening. J Public Health Med 2003; 25:47-52.

33. Wonderling D, Umans-Eckenhausen MA, Marks D et al. Cost effectiveness analysis of the genetic screening program for familial hypercholesterolemia in The Netherlands. Semin in Vasc Med 2004; 4:97-104.

34. National Institute for Health and Clinical Excellence. Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. 2008. http://guidance.nice.org.uk/CG67.

Taylor F, Ward K, Moore THM, Burke M, Davey Smith G, Casas JP, Ebrahim S. Statins for the primary prevention of cardiovascular disease. Cochrane Database of Systematic Reviews 2011, Issue 1. Art. No.: CD004816. DOI: 10.1002/14651858.CD004816.pub4.

Tables and figures

Figure 1

Figure 1, Model structure cascade testing for individual suspected of familial hypercholesterolaemia

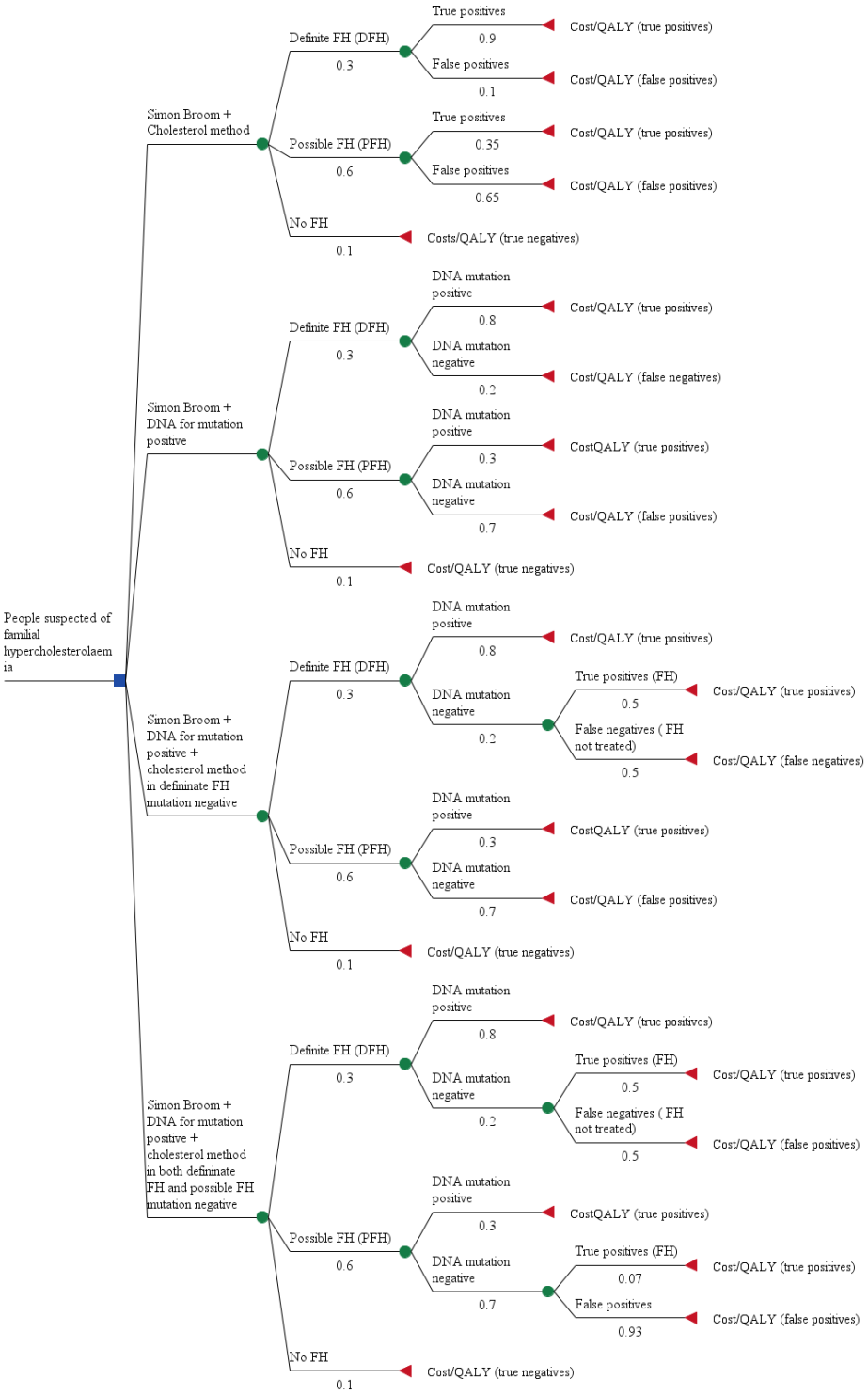
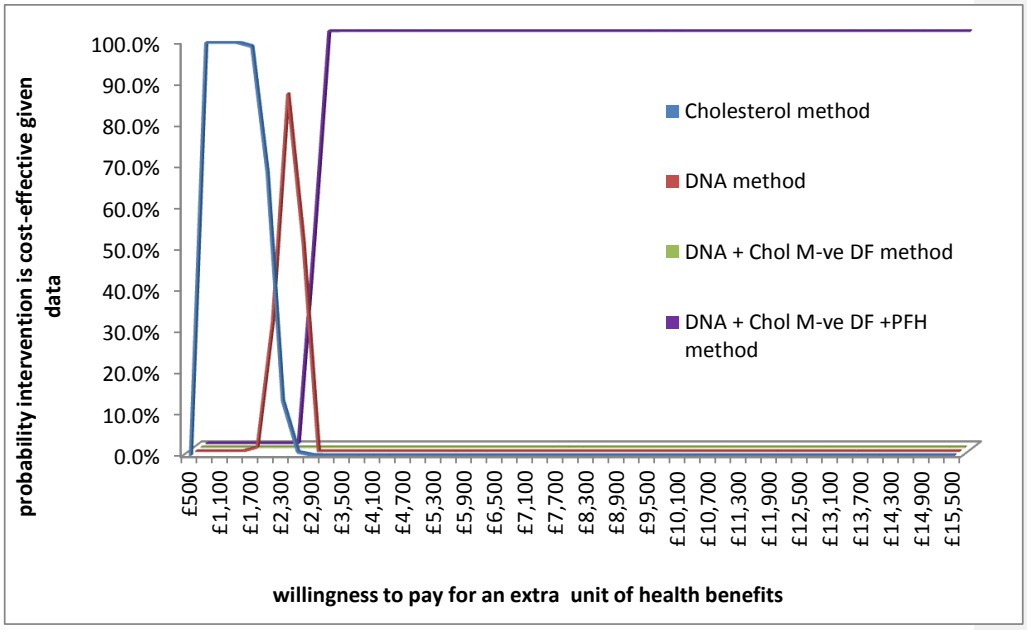

People suspected of familial hypercholesterolaemia
Simon Broom + Cholesterol method
Definite FH (DFH)
0.3
True positives
0.9
Cost/QALY (true positives)
False positives
0.1
Cost/QALY (false positives)
Possible FH (PFH)
0.6
True positives
0.35
Cost/QALY (true positives)
False positives
0.65
Cost/QALY (false positives)
No FH
0.1
Costs/QALY (true negatives)
Simon Broom + DNA for mutation positive
Definite FH (DFH)
0.3
DNA mutation positive
0.8
Cost/QALY (true positives)
DNA mutation negative
0.2
Cost/QALY (false negatives)
Possible FH (PFH)
0.6
DNA mutation positive
0.3
CostQALY (true positives)
DNA mutation negative
0.7
Cost/QALY (false positives)
No FH
0.1
Cost/QALY (true negatives)
Simon Broom + DNA for mutation positive + cholesterol method in defininate FH mutation negative
Definite FH (DFH)
0.3
DNA mutation positive
0.8
Cost/QALY (true positives)
DNA mutation negative
0.2
True positives (FH)
0.5
Cost/QALY (true positives)
False negatives (FH not treated)
0.5
Cost/QALY (false negatives)
Possible FH (PFH)
0.6
DNA mutation positive
0.3
CostQALY (true positives)
DNA mutation negative
0.7
Cost/QALY (false positives)
No FH
0.1
Cost/QALY (true negatives)
Simon Broom + DNA for mutation positive + cholesterol method in both defininate FH and possible FH mutation negative
Definite FH (DFH)
0.3
DNA mutation positive
0.8
Cost/QALY (true positives)
DNA mutation negative
0.2
True positives (FH)
0.5
Cost/QALY (true positives)
False negatives (FH not treated)
0.5
Cost/QALY (false positives)
Possible FH (PFH)
0.6
DNA mutation positive
0.3
CostQALY (true positives)
DNA mutation negative
0.7
True positives (FH)
0.07
Cost/QALY (true positives)
False positives
0.93
Cost/QALY (false positives)
No FH
0.1
Cost/QALY (true negatives)

Figure 2 Cost-effectiveness acceptability curves comparing the four different screening strategies used



Black and white version

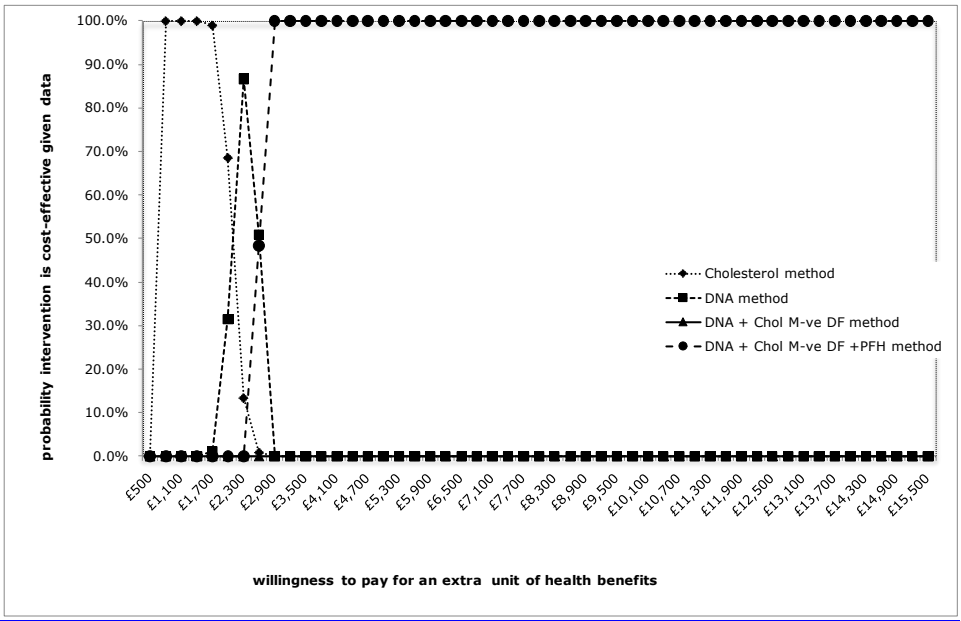


Table 1 Number of index cases and relatives identified by the four cascade strategies

Outcome	**Cascade strategies**			
	cholesterol	**DNA**	**DNA+DFH**	**DNA+DFH+PFH**
Cases (N=1000)				
True Positive	480*	420*	450*	480*
False Negative	0	60	30*	0
False Positive	420*	420	420	420*
True Negative	100	100	100	100
Relatives				
True Positive	765	1338	1385	1433
False Negative	430	0	27	53
False Positive	497	0	33	297
True Negative	2611	1338	1513	2898
Total relatives tested	**4302**	**2675**	**2959**	**4681**

* Probands where cascade testing was undertaken

Table 2: Costs of diagnosis and treatment for each strategy

GRAND COSTS	Cholesterol	DNA	DNA + Chol M-ve DFH	DNA + Chol M-ve DFH +PFH

Total cost of diagnosis	£839	£1,240	£1,280	£1,519
Total cost of treatment	£43,737	£49,677	£51,390	£53,280
Combined total cost	**£44,576**	**£50,918**	**£52,670**	**£54,799**

Table 3, QALY gain per strategy*

	Cholesterol	DNA	DNA + DFH	DNA + DFH +PFH
Total QALY for index cases	8,544	8,517	8,531	8,548
Total QALY for relatives	2,343	15,600	15,754	16,628
Overall total QALYs	**10.89**	**24.12**	**24.28**	**25.18**

*The QALY gain per person were derived from the statin treatment as described in the methods, then multiplied by the numbers screened both for index cases and relatives

Table 4 Incremental costs effectiveness ratios of the DNA based methods compared to each other cholesterol method for screening and identification of FH.

Strategy	Cost	Effects (QALYs)	Incremental cost	Incremental QALYs	ICER (£/QALY)
Cholesterol	£44,576	10.89			
DNA	£50,918	24.12	£6,341	13.23	£479
DNA + Chol M-ve DFH	£52,670	24.28	-	-	ED**
DNA + Chol M-ve DF +PFH	£54,799	25.18	£3,881	1.06	**£3,666**

*** Ruled out by extended dominance*

Supplementary Methods

Model structure, assumptions and analytical methods

We assumed that each index case has five first degree relatives available for testing [16] and each of these five has two first degree relatives (i.e. second degree relatives of the index case), and each of these has two first degree relatives (i.e. third degree relatives of the index case). We also assumed that 65% of the first degree relatives and 60% of the second degree relatives will agree to be tested. These are high estimates for take up in population screening but are based on data from the UK FH Cascade Audit Project FHCAP [S1] study where these values were 85% and 80% respectively. Finally, to simplify the model we assumed that 50% of the tested relatives would be the children of the probands and would be in the age range 18-25 and the remainder would be the siblings of the probands, with an age range of 45-49 years.

We assumed that a monogenic cause underlies a diagnosis of FH, that is, a true FH patient is someone with a relevant gene mutation. To estimate the proportion of true FH patients in the hypothetical 1000 patients referred from general practice, we first used data from FHCAP [S1] in which 30% of the patients currently being treated in lipid clinics had DFH and 60% had PFH while 10% failed to meet either set of criteria. This last group were designated true negative and not considered for cascade testing. Based on reported mutation detection rates, we then assumed that that 90% of those identified as DFH had a relevant gene mutation (were true FH), as well as 35% of those identified as PFH; meaning that 48% of our hypothetical cohort would be true FH patients ((0.9 x 0.3) +(0.35 x 0.6)) We are unaware of any published data to address this directly, and this is an extrapolation from the relative number of mutations identified in DFH and PFH patients (see below).

To estimate the proportion of FH and non-FH relatives that would be identified from true FH index cases with the cholesterol method of screening we used data from the UK[16] and the Netherlands [10], which gave an age-averaged estimate of 32% true positives (i.e. had FH and were identified), 8% false positives (did not have FH but were identified as having FH), 42% true negatives, (did not have FH and were not identified as FH) and 18% false negatives (had FH but were not identified as FH)[10]. From false-positive index cases cascade testing will identify no true-positive relatives, but a proportion will be identified as "affected" (i.e. false-positives) because they have LDL-C levels above the diagnostic cut-offs. Conversely, there will be no cascade screening from false negatives, so some true FH relatives will not be identified.

For the DNA strategy, the mutation detection rate was taken to be 80% in the DFH group and 30% in the PFH group[11, 12,13]. Cascade testing only takes place from mutation-positive index

cases and results in a 50% detection rate (since FH is a monogenic autosomal dominant disorder). However, since current mutation detection methods are not 100% sensitive, a proportion of the mutation-negative index cases will be false negatives. For the DFH group we assumed that this would be true of half of the 20% negatives in the DFH group, meaning that overall 80+10 = 90% of the DFH patients are true positives. For the PFH cases, it was assumed that a similar proportion of mutations would not be detected as in the DFH group (i.e. for every 8 mutations detected in the PFH group one would be missed so the false negative rate in the PFH patients with no detected mutation = 30% x 0.125 = 3.8 mutations per 100 patients), and an upper estimate of 7% of the PFH mutation-negative index cases as false negatives was used.

For the DNA+DFH strategy, as well as mutation positive index cases, cascade testing is additionally undertaken using cholesterol (LDL-C) diagnostic cut-offs in the 20% of patients in whom no mutation has been detected (DFH). The proportions of true- and false-positive diagnoses from this group were estimated as in the cholesterol method. Similarly, for the DNA+DFH+PFH strategy, cascade testing is undertaken using cholesterol (LDL-C) diagnostic cut-offs in the additional group of non-mutation-detected PFH index cases.

Treatment protocol and estimated long-term benefits from statin treatment.

All index cases and relatives with a diagnosis of FH (whether DFH or PFH) are assumed to be offered high intensity statin therapy, in line with NICE guideline on FH[14]. A proportion of those in the DNA-based strategies who do not carry the family mutation will qualify for low intensity statin treatment based on current NICE guidelines of having a >20% 10 year risk of ~~CVD~~[18]CVD [21]. The proportion of such individuals was estimated from data extracted from the Health Survey for England 2003 (Dr Tom Marshall, personal communication). The proportion of ~~such~~ individuals under 40 years is predicted to be 0%. In those aged 40-44 years, it is predicted to be 0.7% in men and 0% in women and in those aged 45-49 years 4.7% in men and 0.4% in women. Since the model includes equal numbers of men and women the average number needing low intensity statin treatment will be 2.6% in those aged 45-49 years. Given that the model is based on equal number of relatives in the 18-25 and 45-49 year age range, overall we predict that 1.3% [17]of relatives will qualify for low intensity statin.

Treatment protocol and estimated long-term benefits from statin treatment.

We developed a Markov model using Microsoft™ Excel to estimate the treatment benefit from statins. The structure of the model is described in detail previously [18]. Data from the Simon Broome database has shown that, compared to the general population, for patients with FH aged below 40 years the relative risk of a cardiovascular event can be as high as 100-fold [7]. For those aged 40-59 years the risk falls to about 4- fold and for those aged over 60 years

the risk is 1.2. In the model we have increased the risk of having a cardiovascular even event by 100, 4 and 1.2 for ages <40 years, 40-59 years and over 60 years respectively for definite FH patients. For relatives who have elevated cholesterol but do not have FH (false positives) their risk was assumed to be 20% more than the general population and to be the same across all age groups. The risk of stroke and peripheral artery disease were assumed to be the same as seen in the general population, because data from the Simon Broome Register indicated that these risks are not significantly higher in the FH ~~population~~[19]population[22]. Death from other causes was assumed to be the same as that of the general population and was taken from the life tables of the England and Wales Government Actuary Department (2006)[20]. The model assumes that risk of cardiovascular disease (CVD) increases with age for both males and females. The rate of CVD increase used in the model was 0.02%, which is the average between males and females reported in the NICE technology appraisal of statins [20]21. Treatment effects of statins were taken from a meta-analysis of the four trials that compared high intensity statins with low intensity statins after myocardial infarction – see table 3 [21]3,[22]24,[23]25,[24]26. We do not believe that this is likely to introduce a significant bias, to the results, because of the extremely high CHD risk in untreated FH patients which is similar to that seen in seen in post MI patients.

Cost data

Drug costs were taken from the BNF [25] [27] (number 61, March 2011) and are shown in supplementary table 5. The proportions of different statins being used to treat FH patients were obtained from clinic data (Dr A Wierzibicki, personal communication). Consultant costs, nurse, clerk, and phlebotomist costs were taken from the standard Unit Costs of Health and Social ~~Care~~[26]Care[28]. Estimates of time taken by each health care professional were provided by the FHCAP study (personal communication). Costs of full fasting and non-fasting cholesterol measurements and costs of CVD events were taken from NHS reference ~~costs~~[27]costs[29]. Cost of DNA testing was £400 and £100 for probands and relatives respectively estimated from the FHCAP study (personal communication). All costs were at 2010/11 prices and as per current NICE guidance; an annual discount rate of 3.5% was used for both costs and health benefits.

Costs of DNA testing for Index cases and relatives were taken from FHCAP study. The costs included the costs of samples; postage in a provided blood-safe GPO recommended container and sending back the processed report to the referring clinicians (total estimated costs £20), For index cases there are costs related to the three stage genetic testing , and for a detailed explanation of the procedures for the 3-stage genetic testing see [S3] The three stages are: 1). ARMS kit test of 20 common mutations, 2) Sequence of *LDLR* gene and 3) MLPA analysis

for deletions, estimated to be about £380 in total. For relatives the direct test for family mutation is estimated to be £80. This gives a total of £400 for index cases (£380 + £20) and £100 for relatives (£80 + £20).

Supplementary References

S1 Hadfield SG, Horara S, Starr BJ et al. Are patients with familial hypercholesterolaemia well managed in lipid clinics? An audit of eleven clinics from the DH FH cascade testing project. Ann Clin Biochem. 2008; 45:199-205.

S2 Government Actuary's Department. Interim Life Tables: Governement Actuary's Department, 2006 http://www.gad.gov.uk/Demography_Data/Life_Tables/Interim_life_tables.asp.

S3 Taylor A, Patel K, Tsedeke J, Humphries SE, Norbury G. Mutation screening in patients for familial hypercholesterolaemia (ADH). Clin Genet. 2010 Jan;77(1):97-9.

Supplementary Table 1, Treatment effect used in the model

Outcome	*Mean*	*Lower 95% CI*	*Upper 95% CI*	*LN(mean)*	*Standard error*
Myocardial infarction	0.81	0.72	0.91	-0.21	0.0610
Stroke	0.82	0.70	0.96	-0.20	0.0822
Peripheral artery disease	0.87	0.69	1.00	-0.14	0.0966
Heart Failure	0.77	0.65	0.92	-0.26	0.0904
Revascularisation	0.78	0.69	1.00	-0.25	0.0966
Unstable angina	0.84	0.71	0.86	-0.17	0.0499
Cardiovascular death	0.92	0.72	1.00	-0.08	0.0855
Death other causes	1.00	1.00	1.00	1.00	1.0000
False Positive	0.95	0.90	0.99	-0.05	0.0248

Log normal distribution was used for treatment effect

Supplementary Table 2: Health state utilities uses in the model

Health state	**Utility**	**Distribution (Beta)**	
		alpha	**beta**
Well	0.95		
Myocardial infarction (first year)	0.76	427.0919	134.8711
Myocardial infarction (subsequent)	0.88	285.9348	38.9911
Stroke (first year)	0.63	91.1103	53.7391
Stroke (subsequent)	0.63	91.1103	53.7391
Peripheral artery disease (first year)	0.90	201.6000	22.4000
Peripheral artery disease (subsequent)	0.90	201.6000	22.4000
Heart failure	0.68	369.0095	171.2680
Heart failure (subsequent)	0.68	369.0095	171.2680
Revascularisation	0.93	31.3118	2.3568
Revascularisation (subsequent)	0.93	40.9973	3.0858
Unstable angina (first year)	0.77	420.1158	125.4891
Unstable angina (subsequent)	0.88	285.9348	38.9911

A beta distribution was used

Supplementary Table 3, Age specific quality of life

Age group	Mean	standard error	alpha	beta
35-44	0.89	0.005	3484.35	430.65
45-54	0.85	0.006	3009.57	531.10
55-64	0.8	0.009	1579.45	394.86
65-74	0.8	0.008	1999.20	499.80
75+	0.76	0.011	1144.89	361.55

A beta distribution was used

Source: DH, Health Survey for England, 1996

The final utility for a health state was age adjusted by multiplying the health state utility with the age utility. For instance

- In general those aged between 45-54 have a utility of 0.85
- If the person has PAD the health state utility is 0.9
- Therefore age adjusted utility in this case for a person with PAD would be (0.85*0.9)=0.765- this is the figure that will be used in the model

Supplementary Table 4 Costs of cardiovascular events

Health state	**Mean Cost**	**Distribution (Gamma)**		**Source**
		alpha	**beta**	
Myocardial infarction (first year)	£1,705	1	1,705	NHS ref cost 2008/09
Myocardial infarction (subsequent)	£500	1	500	Nherera 2010
Stroke (first year)	£10,812	1	10,812	NHS ref cost 2008/09
Stroke (subsequent)	£2,163	1	2,163	NHS ref cost 2008/09
Peripheral artery disease (first year)	£2,214	1	2,214	NHS ref cost 2008/09
Peripheral artery disease (subsequent)	£264	1	264	NHS ref cost 2008/09
Heart failure	£1,798	1	1,798	NHS ref cost 2008/09
Heart failure (subsequent)	£500	1	500	Nherera 2010
Revascularisation	£10,941	1	10,941	DH reference cost
Revascularisation (subsequent)	£500	1	500	Nherera 2010
Unstable angina (first year)	£1,138	1	1,138	NHS ref cost 2008/09
Unstable angina (subsequent)	£500	1	500	Nherera 2010

Gamma distribution was used for costs

Supplementary Table 5, Cost of drugs and proportions of FH who took various drugs

Drug	Proportions of FH on drug	Annual cost	Weighted drug cost in the model**
Simvastatin 40mg	2%	£18	£0.4
Simvastatin 80mg	9%	£43	£4
Atorvastatin 80mg	64%	£368	£235
Simvastatin 40mg + ezetimibe	4%	£436	£17
Simvastatin 80mg + ezetimibe	11%	£537	£59
Atorvastatin 40mg + ezetimibe	10%	£664	£66
Total drug costs	100%		£382.0

Drug cost Source: BNF Vol 59 2010

** *Weighted drug cost in the model is a product of the proportions of people on a drug multiplied by the annual cost of the drug*

Supplementary Table 6, Cost of Cholesterol confirmation method

Healthcare Professional	Unit cost/hr	Time hours (probands)	Time hours (Relatives)	Weighted cost for probands	Weighted cost for relatives
GP practice nurse	£36.00	2	1	£130.00	£65.00
Clerk	£17.00	1	0.5	£17.00	£8.50
Phlebotomist	£17.00	0.17	0.17	£2.89	£2.89
Consultant	£178.00	0.75	0.42	£133.50	£74.76
Non-fasting TC	£7.00			£7.00	£7.00
Full, fasting TC	£8.00			£8.00	£8.00
Letters for relatives	£2.00			£0.00	£2.00
Total cost				**£240**	**£139**

** *Weighted cost in the model is a product of the unit cost/hour multiplied by the estimated time taken for health care professionals*