Appendix E
Health Economic modelling

1 Use of high intensity statin compared to low intensity statin in the management of FH patients

1.1 Introduction

Familial hypercholesterolemia (FH) is a genetic disorder characterized by hypercholesterolemia, xanthomas, and premature coronary heart disease (CHD) [1], [2]. The estimated frequency of FH in western countries is 1 in 500 persons. Heterozygotes typically have values for total serum cholesterol in the range of 7–10mmol/l. Lipid-lowering drug therapy by the statin class of drugs is effective in FH patients and is associated with reduced CHD mortality[3]. Currently in the UK less than 15% of the predicted 110,000 patients are diagnosed [4] and less than 10% are being adequately treated [5],[3]. .

This was identified as a priority for further evaluation because statins were recommended in this guideline as the initial treatment for people with FH due to their effects in reducing morbidity and mortality and the recommended duration of treatment is lifelong. We searched for cost-effectiveness evidence in this population and no studies were found.

Consequently, the GDG requested the development of a de novo economic model to help inform the guideline recommendations.

1.2 Model structure and analytical methods

1.2.1 Population

There is little evidence of the effectiveness of statin use in children thus this model considered adults with heterozygous FH aged 18 years and beyond.

Statins vary in their potency and efficacy with regard to reducing LDL-cholesterol concentrations. For the purpose of this economic model and based on their known differences, statins were categorized as high intensity if they produce greater LDL-cholesterol reductions than simvastatin 40mg (e.g.

simvastatin 80mg and appropriate doses of atorvastatin and rosuvastatin). For a comprehensive analysis of LDL-cholesterol lowering with statins refer to NICE TA094.

The cost-effectiveness of high intensity statins versus low intensity statins is likely to vary by age since the baseline risk of having cardiovascular disease varies by age and sex. However it was acknowledged that the guideline was unlikely to make separate recommendations based on sex thus the model was run separately for different age groups and not by sex.

1.2.2 The choice of comparators

A Markov model was developed to estimate the incremental cost per quality adjusted life year (QALY) of lifetime treatment with high intensity statins atorvastatin 80mg. The GDG decided to consider only high intensity statins that had clinical outcome data for the purpose of modelling. As such atorvastatin 80mg is the high intensity statin used in this model since it is the only high intensity statin with clinical outcome data in patients with stable coronary artery disease, who we assumed had similar prognosis as FH patients. The low intensity statin was simvastatin 40mg or other statins of similar efficacy and costs because this was considered the appropriate initial treatment in the non FH population. The analysis was done from a UK NHS perspective.

1.2.3 Outcomes

The outcomes of interest were death from other causes, and cardiovascular mortality, MI, unstable angina, revascularisation, PAD and stroke. The model did not explicitly include cost impacts of withdrawals, non-concordance or transfers between treatments. The impact of such changes on effectiveness is implicitly included through the use of intention-to-treat trial data. Health outcomes for the cost-effectiveness analysis are summarised in the form of Quality Adjusted Life Years (QALYs), where one QALY represents one year of healthy life.

1.2.4 Model structure and assumptions

In a Markov model there are a finite number of health states. It is assumed that at any point in time, all patients must be in one and only one of the states. The model then replicates how a hypothetical cohort of people moves between the states.

Figure 1 in section 3.2 shows a schematic representation of the patients' pathways. All patients start in the FH state. During each annual cycle of the model, a proportion of patients enter one of the qualifying event health states (MI, unstable angina, stroke, HF, PAD, revascularisation or death) while the remainder stay in the FH state. The model assumes that a person moves from one state to another on the first day of each cycle and remain in that state for the whole cycle. Patients can experience more than one non-fatal event in subsequent periods of the model.

The rate at which people move through the model is regulated by transition probabilities, which describe the likelihood of moving between states over each model cycle (twelve months). These transition probabilities are adjusted for age. The model was run simultaneously for the cohort assuming they were receiving a low intensity statin and then a high intensity statin. For patients on high intensity statins the transition probabilities were adjusted to reflect the expected reduction in cardiovascular events from the clinical trial data. Health care costs and QALYs were then estimated for each option by multiplying the time spent in the various states by mean costs and 'utilities' (health-related quality of life) of the health states. The cost and utility data used in the model was sought from literature. The time horizon modelled is lifetime, with an assumed upper age of 100, by which time all of the cohort have died.

1.2.5 Baseline risks

Baseline risks were taken from the Statins TA 94[6] which shows the prevalence of CHD in the general population. This is obviously different from the population with FH. We applied the age-adjusted risk of cardiovascular

disease reported in the updated Simon Broome paper (Neil 2008)[7]. Thus for ages groups 20-39 we increased the risk of developing cardiovascular disease by a factor of 84.3, for those aged 40-59 a factor of 5.76 was used and those over 60 a factor of 1.2. Stroke and PAD were assumed to be the same as seen in the general population. Death from other causes was assumed to be the same as that the general population and was taken from the life tables of England and Wales[8]. See **Error! Reference source not found.** in section 1.11 for baseline data used in the model.

The model assumes the risk of CVD in the general population increases with age. The NICE statins technology appraisal (TA 94) used data from the Health Survey for England 1998, and estimated a mathematical relationship between age and risk increase. For all males (all males, non-diabetic males and diabetic males) a linear relationship was the best fitting mathematical model and the slope of the linear relationship was 0.0003. This represents an increase in the one year risk of 0.03% for a one year increase in age. For all females the slope was 0.00008. The rate of increase used in the model is therefore 0.0002 which was the average between males and females.

1.2.6 Treatment effects

There was no trial evidence considering high intensity statins with low intensity statins in FH patients. The only available evidence was observational data from the Simon Broom register which showed benefit from treatment before and after the use of statins. For the main analysis we assumed that FH patients do not benefit differently from statin treatment from patients with after myocardial infarction with stable coronary disease (CAD). This enabled us to use reduction in cardiovascular events reported by the TNT (LaRosa (2005)[9] and IDEAL (Pedersen 2005)[10] trials which we meta-analysed and used in sensitivity analysis. We then used data from the Simon Broome[7] in sensitivity analysis to estimate statins benefit.

Cost data

Total costs of interventions should include the direct cost of drug treatment and also potential savings from avoided treatments due to reduced incidence of cardiovascular disease. Costs were calculated using cost for each of the health states of the model, multiplied by the time spent in each state. Costs were at 2007-08 prices. As per current NICE guidance[11], an annual discount rate of 3.5% was used for both costs and health benefits.

Estimates of costs were taken from the literature or NHS reference cost[12]. Drug costs were taken from the prices quoted by the drug tariff, Prescription Pricing Authority (PPA)[13]

1.2.7 Health related quality of life (health state utility)

In the NICE reference case, the value of health outcomes – including beneficial and harmful impacts of treatment on mortality and morbidity – is estimated using the Quality Adjusted Life Year (QALY) approach. This requires estimates of survival and quality of life associated with each health state included in the model. Utility data was obtained from published literature.

Utilities were adjusted to reflect the fact that health-related quality of life in the general population decreases with age (i.e. multiply the disease utility weight by age utility weight). Age utility weights were taken from the Department of Health, Health Survey for England (1996)[14].

Statin therapy may be expected to have two opposing effects on quality of life: i) improvements through the reduced incidence of cardiovascular events and ii) reductions in quality of life through the impact of treatment-related adverse effects. Differences in adverse effects between high and low intensity statins can have an influence on their relative cost-effectiveness. However there are no published studies that have quantified the difference in quality of life due to treatment side effects. Published studies suggest that there is no difference in quality of life between high intensity when compared with low intensity

statins. We thus assumed that high intensity statins will not result in loss of quality of life for the base model.

1.2.8 Cost-effectiveness

The results of cost-effectiveness analysis are presented as Incremental Cost-Effectiveness Ratios (ICERs), which determine the additional cost of using high intensity statins per additional QALY gained compared with low intensity statin

ICERs = (cost of high intensity statins – cost of low intensity statins)/ (QALY of high intensity statins – QALY of low intensity statins of statins)

1.2.9 Sensitivity analysis

The model includes a base case analysis supplemented with univariate deterministic sensitivity analyses to test the impact of uncertainty over various model parameters and assumptions.

1.3 Results

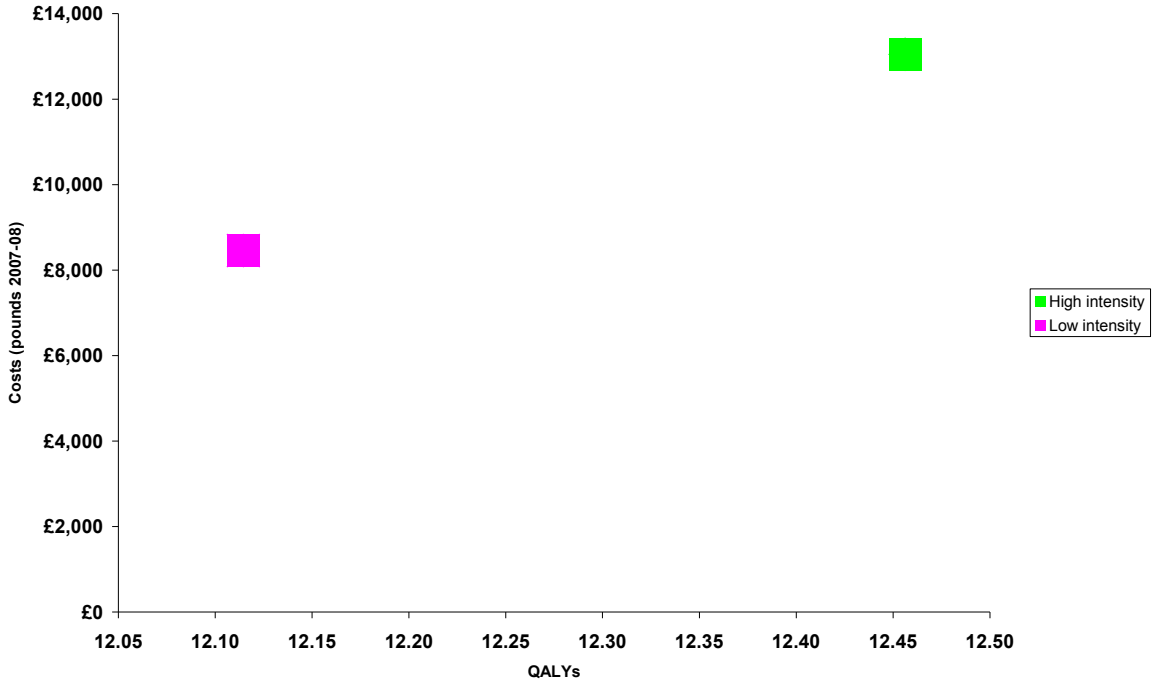
The base case results are presented below, and cost-effectiveness is assessed against a threshold of £20,000/QALY.

Table 1 indicates the modeled number of events for the hypothetical 1,000 patient who are taking high intensity or low intensity statins. The table indicates that fewer cardiovascular events occur in the population treated with high intensity statins. More people will die from other causes and fewer people will die from cardiovascular mortality. This translates to a gain of 0.34 discounted QALYs when compared with low intensity statins.

Table 1 Lifetime event outputs modelled for a cohort of 1,000 patients high intensity statins compared with low intensity treatment strategy for patients with FH

Health state	Low intensity	High intensity
MI	443	348
Stroke	313	251
PAD	66	67
Heart failure	220	153
Revascularisations	266	203
Unstable angina	140	117
Cardiovascular mortality	370	329
Death from other causes	612	650

Scatter Plot, showing the costs and QALY gain for an average 50 year old patient with FH.



The scatter plot shows patients on higher intensity statins will benefit more than those on lower intensity. The additional benefit is achieved at an additional cost.

1.3.1.1 ***Cost-effectiveness results of high intensity statins compared with low intensity statins in FH patients***

The incremental cost per patient needed to achieve the net gain of 0.34 QALYs is estimated to be about £4,591. The estimated ICER was about £13,437/QALY. High intensity statins are cost-effective for an average FH patients using £20,000/QALY threshold.

Table 2, Cost-effectiveness results of high intensity statins compared with low intensity statins in FH patients

	Cost (£)	Effect (QALYs)	Incremental cost (£)	Incremental effect	ICER (£/QALY)
Low intensity	£8,457	12.11			

High intensity	£13,047	12.46	£4,591	0.34	£13,437

1.3.2 Sensitivity analysis

A range of univariate sensitivity analyses were conducted to assess the impact of different input parameters on the base case results. In these analyses we change one parameter at a time holding other parameters constant at their base case values. The results are interpreted using a cost-effectiveness threshold of £20 000 per QALY.

1.3.2.1 Efficacy of treatment (using lower and upper confidence intervals)

The efficacy of high intensity compared to low intensity was assessed using the upper and lower 95% confidence intervals from the meta-analysis. The model became more cost-effective when the treatment effects were improved (set to their lower confidence interval) and worsened (upper confidence interval) for all outcomes. The ICERs when the upper confidence interval of CVD deaths is used, the high intensity results in more CVD deaths than the low intensity treatment and the high intensity becomes dominated by low intensity. This result implies the high intensity resulted in higher costs and less benefits than the low intensity. The model is thus sensitive to assumptions about treatment effect on mortality.

Table 2 Efficacy of treatment (using lower and upper confidence intervals)

Outcome	Mean (95% CI)	Lower limit ICER	Upper limit ICER
Non-fatal MI	0.81 (0.72-0.91)	£11,890	£15,556
Non-fatal stroke	0.82(0.70-0.96)	£11,146	£16,747
Non-fatal PAD	0.87(0.69-1.11)	£12,464	£14,975
Heart Failure	0.77(0.65-0.92)	£12,580	£14,679
Revascularisation	0.78(0.71-0.86)	£12,984	£13,968
Unstable Angina	0.84(0.69-0.1.01)	£12,430	£14,674
CVD mortality	0.92(0.72-1.171)	£7,579	**D****

D** High intensity is dominated by lower intensity. RR of CVD mortality is 1.17 suggesting there are more deaths in high intensity statin arm.

*1.3.2.2 **Results by age***

The model results suggest that higher intensity statins are cost-effective for ages below 60 years when compared to low intensity statins Beyond 60 years, high intensity statins are no longer cost-effective

Table 3 Effect of age on cost-effectiveness using the price of atorvastatin 80mg

Age	Cost/QALY (ICER)
20-39	£19,649
40-59	**£13,437**
60-74	£26,254
Over 75	£33,569

Cost of high intensity statins (assuming price of atorvastatin fall to the level of generic simvastatin 80mg)

Our model used efficacy data from atorvastatin 80mg for high intensity statins and thus used the price of atorvastatin 80mg. If we assume a price fall to that of generic simvastatin 80mg, high intensity will dominate lower intensity for people aged upto 74 years. For those aged over 75 years the ICER is £800/QALY. This analysis suggests that price of statins is one of the main cost-effectiveness drivers.

Table 5, Cost of high intensity statins (assuming price of atorvastatin fall to the level of generic simvastatin 80mg)

Age	Cost/QALY (ICER)
20-39	D
40-59	**D**
60-74	D
Over 75	£800

D= high intensity will dominate lower intensity statins

*1.3.2.3 **Results for males/females of all age groups, relative risk of CHD mortality***

In the base model we assumed that people with cardiovascular disease have the same risk of dying from other causes compared with the general

population. This was a conservative assumption. Packham et al[15], and Robinson et al[16], demonstrated that this could be two fold or more In sensitivity analysis we assumed that there was two fold risk of dying from other causes for people with stable coronary heart diseases. The ICERs increase slightly to about £15,454/QALY when the risk is assumed to be two, but still below the £20,000 threshold.

*1.3.2.4 **Discounting***

Discounting is a technique which allows the calculation of present values of costs and benefits which accrue in the future. Discounting is based on a time preference which assumes that individuals prefer to benefits now rather than latter, and by the same reasoning, individuals prefer to delay costs rather than incur them in the present. The strength of this preference is expressed by the discount rate which is inserted in economic evaluations. NICE recommends we discount both cost and benefits at 3.5%.

We tested two different scenarios i.e. no discounting and a 5% discount rate. The model was not sensitive to assumptions about discounting. When there is no discounting performed, the ICERs fall and when the discount rate increases the ICERs increase as shown in the table below.

Table 6 Results for males of all age groups, impact of discounting

Age	no discounting (ICER)	5% Discount rate (ICER)
40-59	£10,043	£15,155

*1.3.2.5 **Health state utilities and costs of cardiovascular events***

The health state utilities used in the model were obtained from the literature. We tested the assumption that the mean health state utilities were 0.2 less or more than those obtained from the literature. The costs of cardiovascular events were increased by 100% and reduced by 50% (GDG assumption). In all cases the model results were not sensitive to changing assumptions about quality of life estimates and costs of cardiovascular events and ICERs ranged between £13,000 and £15,000/QALY.

Using efficacy data from the Simon Broome database

The base model used efficacy data from IDEAL and TNT trials. In sensitivity analysis we used efficacy data from the longitudinal database. The results from the analysis showed that efficacy of statins was different for different age groups, see table 10 in appendix. High intensity statins were cost-effective with an estimated ICER of about £4,000/QALY

1.4 Discussion and limitations

Our model results demonstrate that the incremental cost per patient on atorvastatin 80mg needed to achieve the net gain of 0.34 QALYs is estimated to be about £4,591 when compared with low intensity statins. The estimated ICER is about £13,437/QALY suggesting that high intensity statins are cost-effective. The results are sensitive to age, cost of statins and treatment effect.

Rosuvastatin was not considered on the grounds that it did not have clinical outcome data, however assumptions can be made about its cost effectiveness based on its efficacy in reducing cholesterol from the STELLAR trial. Assuming the reduction in cholesterol translates to reduction in final outcomes, Rosuvastatin will be cost effective. A threshold analysis showed that as long as rosuvastatin was more than 0.7% more effective (In the STELLAR trial, rosuvastatin is said to be 8.2% more effective in lowering cholesterol than Atorvastatin 80mg, then the choice will be Rosuvastatin 40mg.

If it is assumed that Simvastatin 80mg was has the same effectiveness as Atorvastatin 80, then Simvastatin 80 will be more cost effective as it is cheaper than Atorvastatin 80. If however it is assumed that Simvastatin 80mg was 5% less effective (as in the Stellar study) than Atorvastatin 80mg, the result is high intensity treatment will dominate low intensity treatment.

Due to a lack of data on the effectiveness of simvastatin and rosuvastatin at maximal dose, and lack of credible safety data for atorvastatin, simvastatin and rosuvastatin at these doses, the incremental cost effectiveness was not

further examined. If high intensity treatment with Simvastatin 80mg, Atorvastatin 80mg, Rosuvastatin 40mg are considered individually, they are all cost effective options compared to Simvastatin 40mg.

The effect of age is not unexpected since younger patients have a much bigger risk if left untreated. For instance, if untreated the risk of cardiovascular disease is about 84 times more than the general population[7] for those aged less than 40 years compared to an increased risk of 20% for those aged over 60 years. Thus if patients are on atorvastatin 80mg, the ICERs for those aged over 60-74 years is about £26,000/QALY.

One of the main limitations of our model is the lack of long term outcome trials in the use of statins in the treatment of patients with FH. We assumed that FH patients will not benefit differently from statins when compared with patients post MI. Thus trial data from MI patients was meta-analysed to derive treatment effect of statins. There is also lack of long-term safety and utility data for high intensity statins in trials. The trials reported that there was no significance difference between high and low intensity with regards to major side effects. However the GDG is aware of issues with the recruitment of the post MI trials TNT[9] and IDEAL[10] which only include people who could tolerate the statins hence the finding of no difference may be confounded by this. Our model assumed that there would be no loss in utility due to treatment side effects which may not be the case. In this respect our model may overestimate the cost-effectiveness of high intensity statins (make them look more favorable)

Another limitation of the model arises because of the nature of Markov models. These assume that the probability of an individual moving to any given health state in one time period depends only their current health state (there is no longer 'memory' in the model). Thus the probability of heart failure for a patient whose last CVD event was an MI is assumed to be the same irrespective of how many CVD events they have previously had. 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 overall costs and overestimate health outcomes for the cohort. Thus, interventions that prevent more CVD events will tend to appear rather less cost-effective than they may be in reality. So the model is conservative in this respect.

The model did not directly address the issue of treatment of withdrawals and non-concordance with treatment. Since the treatment effects are based on 'intention-to-treat' analyses, the impact of withdrawals and non-concordance from the trials is already included in the model. However, the model continues to attribute drug costs for all patients throughout their lifetime. This is a conservative assumption that will tend to underestimate the cost-effectiveness of treatment. On the other hand, concordance and continuation of treatment may well differ between the trial context and routine practice.

1.5 Conclusions

In conclusion, atorvastatin is cost-effective for the treatment of FH for those aged less than 60 years. However when the cost of atorvastatin 80mg was assumed to be the same as that of generic simvastatin 80mg, high intensity statins became cost-effective for all age groups.

Cascade testing for FH using DNA testing and low density lipoprotein (LDL) Cholesterol methods

1.6 Introduction

Familial hypercholesterolemia (FH) is a genetic disorder characterized by hypercholesterolemia, xanthomas, and premature coronary heart disease (CHD)[1] and[2]. The estimated frequency of FH in western countries is 1 in 500 persons. Heterozygotes typically have values for total serum cholesterol in the range of 7–10mmol/l. Efficient lipid-lowering drug therapy by the statin class of drugs is effective in FH patients and is known to reduce CHD mortality[3]. Currently in the UK less than 15% of the predicted 110,000 patients are diagnosed, Marks et al[4] and less than 10% are being adequately treated LIPID Study Group 1998[5],[3]. FH is caused by mutations in three different genes, namely those coding for the receptor for low density lipoprotein (LDL) particles (*LDLR*) for the major apolipoprotein of the LDL particle apolipoprotein B (*APOB*) and for an enzyme involved in the degradation of the receptor as it recycles, *PCSK9*[2].. The availability of DNA diagnosis at an asymptomatic stage and of effective lipid lowering therapy support the utility of cascade testing for FH[17] In 1994 an FH testing programme was started in The Netherlands; this programme actively approaches first and second degree relatives of index patients with a known mutation for testing, after informing them about their possible risk a process known as “cascade testing”[18]

In the UK, FH is diagnosed by clinical criteria based on lipid levels, family history, and presence of xanthomas[19]. Individuals fulfilling these criteria are given the diagnosis of definite FH (DFH), while those showing elevated lipid levels and family history only are given the diagnosis of possible FH (PFH). Depending on the sensitivity of the methods used for mutation screening, a mutation causing FH can be identified in 60-80% of DFH patients[2;20] but only 20-30% of PFH patients[21] suggesting that many of the latter do not have monogenetic FH. Once the underlying mutation has been identified in an

index patient, molecular genetic screening of first degree relatives has a sensitivity and specificity close to 1.0, and this makes misclassification a rarity. In contrast, when based on lipid levels, where typically the ninety-fifth percentile of total serum cholesterol or LDL-cholesterol (LDL-C) is used as a cut-off value, misclassifications will occur in 15–30% of the patients[22-24]. Because of within-individual fluctuations and because of change over time, some individuals will move from below to above the cut-off value on repeat measurements, while a DNA test is unambiguous and is only required once. Thus, if the diagnosis is made solely by lipid levels classification errors will occur, and as well as some FH patients being given a false negative diagnosis, cascading from false positive subjects will reduce the efficiency of cascade testing. The aim of the analysis was to compare the costs and benefits in terms of QALY gained of finding the relatives of index patients with FH using cascading testing, and comparing the strategies of the use only of LDL-C levels for diagnosis, versus the use of DNA methods alone, or a combination of both.

This was selected as a priority for further evaluation because this approach was recommended as for the identification of people with FH and the cost differentials between the alternative approaches (e.g. cholesterol testing or DNA testing) were considerable as was the potential eligible population.

1.7 Model structure and analytical methods

Treatment protocol

All index cases with a diagnosis of FH (whether DFH or PFH) will be offered high intensity statin (HIS) therapy, in line with our earlier health economic modelling where this was shown to be cost-effective. In all strategies, all relatives identified as having elevated LDL-C are offered lipid-lowering therapies, and those with a diagnosis of FH (by carrying the family mutation in the DNA-based strategies or by LDL-C measures in the Cholesterol-based

strategies) will be offered HIS. A proportion of those in the DNA-based strategies who do not carry the family mutation will qualify for Low Intensity Statin (LIS) treatment based on current NICE guidelines of having a >20% 10 year risk of CVD. The proportion of such individuals was estimated from data provided by Dr Tom Marshall extracted from the Health Survey of England 2003. As shown in the Table below, the proportion of such subjects in the under 30 years age is predicted to be 0%, while in the 45-49 year age group this is predicted to be 4.7% in men and 0.4% in women, so based on an expectation of equal numbers of men and women the average number needing LIS treatment will be 2.6%. Since 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% of relatives will qualify for LIS, and in sensitivity analysis we tested 0%, 5% and 100%

Table 7, The proportion of persons aged 30 to 75 at ≥20% ten-year CVD risk

Age	Men	95% CI	Women	95% CI
30-34	0.0%	(0.0%-0.8%)	0.0%	(0.0%-0.7%)
35-39	0.0%	(0.0%-0.7%)	0.0%	(0.0%-0.6%)
40-44	0.7%	(0.0%-1.7%)	0.0%	(0.0%-0.6%)
45-49	4.7%	(2.0%-7.4%)	0.4%	(0.0%-1.2%)
50-54	14.3%	(9.9%-18.7%)	3.4%	(1.2%-5.6%)
55-59	35.6%	(29.5%-41.7%)	4.2%	(2.0%-6.5%)
60-64	60.5%	(53.2%-67.8%)	13.9%	(9.5%-18.3%)
65-69	74.3%	(67.2%-81.4%)	24.0%	(17.9%-30.2%)
70-74	88.9%	(83.2%-94.6%)	43.9%	(36.1%-51.7%)

This is based on the Health Survey for England 2003. It includes 4264 persons aged 30 to 74 with complete risk factor information, and excludes those with a current diagnosis of Cardiovascular Disease or Diabetes.

Model Structure

For the cost-effectiveness analysis, four different strategies were compared. The standard method of clinical diagnosis and identification of affected relatives using elevation of LDL-C levels was the base line comparator, and is referred to as the "Cholesterol" method. The UK FH Cascade Audit Project (FHCAP) has confirmed that, based on the Simon Broom criteria, 30% of the patients currently being treated in lipid clinics have DFH and 60% have PFH while 10% fail to meet either criterion Hadfield et al {7952}. Only patients meeting the criteria of DFH or PFH were included for cascade testing. The second strategy is based on the identification of an FH-causing mutation by molecular genetic methods, and is called the "DNA" method. Here, only patients with an identified FH-causing mutation will be included for cascade testing, and the relatives tested for the family mutation. This is the model used in the Netherlands {1616}. All relatives with elevated LDL-C levels are offered appropriate treatment (HIS if they carry and LIS if they do not carry the family mutation), but further cascade testing is *only* carried out from mutation-positive subjects. Two variant strategies of the DNA method were also examined. In the strategy 3, following DNA testing of the index cases cascade testing of relatives is undertaken in all mutation-positive index cases as above (i.e. using the DNA information to offer appropriate lipid-lowering treatment and to select those from whom secondary cascading will be undertaken), and additionally, in the relatives of only DFH index cases where no mutation can be found, cascade testing is undertaken using measures of LDL-C levels to identify "affected" relatives for treatments and for secondary cascading (DNA+DFH method). In the final strategy, cascade testing is undertaken in all mutation-positive index cases (as above) and additionally from *both* DFH and PFH index cases using LDL-C measures (DNA+DFH+PFH method).

Diagnostic Definitions

As shown in Table 1, for the purposes of the analysis a true-positive index case is defined as one who has a monogenic cause of FH who is selected for cascade testing, while a false-positive case is defined as one who does not actually have a monogenic cause (i.e. fulfils the clinical criteria of FH but the cause is due to polygenic plus environmental causes) but who is selected for cascade testing. A false-negative index case is one who is not selected for cascade testing but who actually does have a monogenic cause of FH, and a true-negative index case is defined as one who does not actually have a monogenic cause, and who is not selected for cascade testing (i.e. does not fulfil the clinical criteria of FH).

For relatives, a true-positive is defined as one who has a monogenic cause of FH who is correctly identified by the strategy in use (i.e. by elevated LDL-C levels or by being a carrier for the family mutation) and who is offered treatment and selected for cascade testing. A false-positive relative is defined as one who does not actually have a monogenic cause but who is offered treatment and selected for cascade testing (i.e. has LDL-C levels above the diagnostic cut-off for age and gender but the cause is due to polygenic plus environmental causes). A false-negative relative is one who actually does have a monogenic cause of FH but who is not offered treatment or selected for cascade testing (i.e. with LDL-C levels below the diagnostic cut-off for age and gender due to “protective” polygenic plus environmental causes), and a true-negative relative is defined as one who does not have a monogenic cause, and who is not offered treatment or selected for cascade testing (i.e. with LDL-C levels below the diagnostic cut-off for age and gender or who does not carry the family mutation).

Costing

The model estimates the incremental cost-effectiveness of cascade testing using these different approaches, using data on the cost of identification of index cases and relatives from the recently completed DH UK FH cascade audit project (UKFHCAP), and up-to date figures for the costs and effectiveness in reducing CHD mortality and morbidity of statins {5399}. In the base model it was assumed that 65% of the first degree relatives and 60% of the second degree relatives will agree to testing. These estimates are high for the take up in population screening but, the GDG recommended their use based on data from the FHCAP where these values were 85% and 80% respectively. The impact on cost-effectiveness of changing the take up rate for index cases and subsequent relatives was tested in sensitivity analysis (http://www.londonideas.org/internet/FHCascade/FH_Recommendations_Sept07.pdf)

Decision Tree

A decision tree was constructed in Excel where a hypothetical 1000 patients referred from General Practice with a suspicion of heterozygous FH entered the model. The structure and the proportions of patients in the different arms of the decision tree was agreed by the GDG and is shown in Figure 4 in the appendix, with four strategies being compared as described above. A decision node (square) is placed directly following the diagnostic dilemma being resolved. Chance nodes (circles) represent uncertain outcomes of each of these decisions. Probabilities of branches coming off the chance node add up to one. A terminal node (triangle) is reached when all outcomes for a particular pathway have been accounted for. It was assumed that every index case has five first degree relatives that are tested, 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). Sensitivity analysis was carried out comparing cascading to third degree relatives and only to second degree relatives

Assumptions for the relative proportions in all branches were reached from the available published data and from assumptions agreed by the GDG. For the Cholesterol method, it was assumed that 90% of the DFH and 35% of the PFH are true FH (i.e. 270 + 210), and 10% and 65% respectively are false positive (30 + 390 respectively). 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). The relative proportion of “FH” and non-FH relatives from the true FH index cases was estimated from the FHCAP data and analysis of the Netherlands relative data set {5398}. This showed that using as a diagnostic cut-off the intersection between the distribution of LDL-C levels in mutation-carriers and non-carriers results in a false positive identification rate of 14.9% in 15-24 year olds and of 16.3% in 45-55 year olds, and a false negative rate of 28.9% and 42.4% respectively (cut-offs for Males and Females 3.01/4.31mmol/l and 3.32/4.05 respectively). Based on the assumption of equal numbers of 15-24 year old and 45-55 year old relatives, these were used to derive the following age-averaged rates; True+ve 32%, False+ve 8% True–ve 42%, False–ve 18 (Starr et al 2008). From false-negative 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 (estimated as above to be 14.9% in 15-24 year olds and 16.3% in 45-55 year olds Similar proportions were used for the second and third degree relatives.

For the DNA strategy, the mutation detection rate in DFH was taken to be 80% {1280} {1542}, {5395}. 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). Since current mutation detection methods are not 100% sensitive, a proportion of the mutation-negative index cases are false negatives. For the DFH group this was assumed to be 50%, meaning that overall 90% of the DFH patients are true positives (the figure used for the Cholesterol strategy). For the PFH cases, where the reported

mutation detection rates range between 25-50%, it was assumed that a similar proportion of mutations would not be detected as in the DFH group (i.e. roughly 1 in 8) and an estimate of 7% of the PFH mutation-negative index cases as false negatives was used.

For the DNA+DFH strategy, cascade testing is additionally undertaken using LDL-C diagnostic cut-offs in all 60 no-mutation DFH patients (of whom 50% (i.e. 30) are true-positive and 50% (i.e. 30) are false-positive. The proportions of “affected” and “non-affected” FH relatives (and the proportion of true- and false-positive diagnoses) from these two groups were estimated as in the Cholesterol method. Similarly, for the DNA+DFH+PFH strategy, cascade testing is undertaken using LDL-C diagnostic cut-offs in the additional group of 420 non-mutation PFH index cases, of whom 7% (i.e. 30) are true positive and 93% (i.e. 390) are false positive.

Estimation of treatment benefit from high compared to low intensity statins trials

A Markov model was developed using Microsoft™ Excel to estimate the treatment benefit from statins. The structure of the model was agreed by the GDG. This enabled the calculation of long-term outcomes of lifetime statin treatment for the management of FH from a UK NHS perspective. Eight health states were modelled; Well (no event), unstable angina, myocardial infarction (MI), PAD stroke, heart failure, revascularisation, cardiovascular death and death from other causes All patients start in the well state, with the risk of developing any of the other health states. Baseline risks were taken from the Statins TA 94 {5230} and are shown in the table 1 in the appendix E, by age. The risk of developing a cardiovascular event varies with age for FH patients.

Data from the Simon Broome database has shown that, compared to the general population, for patients aged below 40 years the relative risk can be as high as 125 for females {5397}. For those aged 40-59 years the risk falls to about 6 fold and for those aged over 60 years the risk is about 1.2 compared to the general population. In the model we have increased the risk of having a CVD event by 84.3, 5.67 and 1.2 for ages <40 years, 40-59 years and over 60 years respectively {5399} for definite FH patients. For relatives who have elevated lipids but do not have FH (false positives) their risk was assumed to be 20% more than the general population and the same across all age groups (GDG assumption). Rates of PAD, stroke and TIA were assumed to be the same as the general population, based on Simon Broome data {5397}

Cost data

Drug costs were taken from the prices quoted by the Prescription Pricing Division {7799} (see table 7 in appendix E). The proportions of different statins being used to treat FH patients were obtained from Dr Anthony Wierzbicki (personal communication). Consultant costs, nurse, clerk, phlebotomist costs were taken from Curtis at al 2007 {7791} (see table 13 in appendix E). Estimates of time taken by each health care professional were provided by the FHCAP study and the GDG members (personal communication). Costs of full fasting and non-fasting cholesterol measurements were taken from the updated HTA (personal communication Dr Marks) and from the experience of GDG members. Costs of CVD events were taken from the statin TA 94 {5230} and adjusted for inflation. All costs were at 2007 prices. 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 MI, stroke, heart failure, TIA, PAD, unstable angina, revascularisation, cardiovascular and total mortality. We obtained utility weights for each health state from the literature, see table 16 in appendix E. Health survey of England 1996 data showed that in general utility falls by age. We adjusted the utility values we found from literature for age; by multiplying the health state utility weights by the utility of each age in the general population (see table 17 in appendix E). Thus the model uses age-adjusted utilities. The beneficial value of health outcomes (but not the potential harmful impacts of treatment which for stains are rare) was estimated using the Quality Adjusted Life Year (QALY)

Cost-effectiveness:

The results of cost-effectiveness analysis are presented for a 50 year old index case and a 30 year old relative. This 30 year estimate is the rough average age of the five first degree relatives of the index case, based on the model family used with on average two siblings of similar age, and two children of 18 year age (plus one living parent. The results are presented as discounted Incremental Cost-Effectiveness Ratios (ICERs), which determine the additional cost of using one strategy (for instance the DNA method) per additional QALY gained compared with the baseline strategy (Cholesterol method).

Where more than two interventions are being compared, the ICERs are calculated using the following process: 1) The interventions are ranked in terms of cost (from the cheapest to the most expensive); 2) If an intervention is more expensive and less effective than the previous one, then it is said to be 'dominated' and is excluded from further analysis; 3) ICERs are calculated for each intervention compared with the next most expensive non-dominated option. If the ICER for an intervention is higher than that of the next more effective strategy, then it is ruled out by 'extended dominance'. This means that there is some mixture of two other strategies that is more effective and less expensive; 4) ICERs are recalculated excluding any options subject to extended dominance. {7790}

Sensitivity Analysis:

The model included a base case analysis and was supplemented with univariate deterministic sensitivity analyses to test the impact of uncertainty for various model parameters and assumptions.

1.8 Results

Table shows the numbers of true- and false-positive and negative FH identified by each strategy. For each method, starting with a hypothetical

1000 suspected FH patients, and based on the FHCAP data, 30% will be DFH and 60% will be PFH. 100 will not meet the diagnostic criteria of DFH or PFH and no cascade testing is carried out from them. Based on assumptions agreed by the GDG, these are all classified as true-negatives. It is possible that 1-2 of these individuals may actually have FH and would therefore be incorrectly classified as such, but this would be the same for each strategy and so would not impact on the relative cost-effectiveness comparisons. Of the 300 DFH 90% (i.e. 270) are true-positives while 35% of the PFH (i.e. 210) are true-positives.

For the Cholesterol method, based on the false-positive and false-negative rate of LDL-C cut-offs (using the "gold-standard" of mutation carrier status in the Netherlands relative data set[28], the three rounds of cascade screening would entail the testing of 4302 relatives, of whom 18% will be true-positives, 11% false positives, 61% true-negatives and 10% false-negatives. The low overall proportion of relatives designated as positives is due to several reasons. Firstly, while a small proportion of DFH index cases are false-positives (10%), a large proportion of PFH are false-positives (65%), and no true FH relatives can be identified by cascading from false-positive index cases. Secondly, because of the overlap between LDL-C levels in mutation-positive and non-mutation relatives[28], many false-positive and false-negative diagnoses based on LDL-C cut-offs will occur, with a false-negative rate of >45% in 45-55 year-olds (i.e. in the siblings of the index case). Finally, the consequence of this is that while many affected people will thus be mis-classified (and not cascaded from and their at-risk relatives not identified), many non-FH relatives will incorrectly be selected for further cascade testing and no true-positive relatives will be detectable from such cascading. A further consequence for the 430 false-negative individuals is that they may not be offered the appropriate level of care required for adequate management of their FH.

For the DNA method, cascading takes place from all 420 mutation-positive index cases (240 from DFH and 180 from PFH, based on the predicted

mutation detection rate in these groups). Each of these has five first degree relatives of whom 50% are mutation-carriers, each of whom has two first degree relatives of whom 50% are carriers and similarly for the third round. This result in testing 2675 relatives of whom 50% is mutation-positive. A proportion of the relatives are identified as having elevated CHD risk according to NICE guidelines and are offered appropriate lipid-lowering therapy (approximately 1.3% (GDG estimate). Costs for this are included in the modeling, but because they do not have FH they are likely to need only a low dose of statin to achieve adequate response. Since they do not carry the family mutation no cascade testing from them is carried out and their relatives are not tested. However, 30 of the DFH and 30 of the PFH index cases are false-negative cases because mutation detection methods are not 100% sensitive, and thus the opportunity to cascade test from these cases is missed (6.6% of the 900 sent for DNA testing).

For the DNA+DFH method, cascading takes place from all 420 mutation-positive index cases (with affected relatives identified based on DNA results) plus from all the 60 remaining non-mutation DFH index cases. 50% of these are false-negative and 50% are false positive FH cases, and identification of their “affected” and “unaffected” relatives occurs using LDL-C cut-offs. This results in the proportions of false-positive and negative relatives as for the Cholesterol method, and overall the number of tested relatives increases by 11%, with the number of true-positives increasing by 3.6%, and with 33 relatives receiving a false-positive diagnosis (1% of the total tested). For the DNA+DFH+PFH method the approach is the same, with cascading taking place from an additional 390 mutation-negative PFH index cases. 7% of these are false-negative and 93% are true-negative FH cases. Overall the number of tested relatives increases by 72% compared with the DNA method, and by 13.6% compared with the Cholesterol method, because of the higher number of true-positives identified by the DNA method who are subsequently included in secondary and the tertiary cascading. Compared to the DNA+DFH method, the number of true-positive relatives identified increases

by 2.6%, and the number of false-positive relatives identified increases by nine fold, although this still represents only 5.5% of the total number of tested relatives and is less than the 10% figure for the Cholesterol method.

Table 8Total numbers of index cases cascaded from, number of relatives tested in each strategy and numbers predicted to be "affected" and "non-affected" with FH

	Statin used	Cholesterol	DNA	DNA + DFH	DNA+DFH +PFH
INDEX CASES					
Total tested		**1000**	**1000**	**1000**	**1000**
True positives - FH, cascaded	HIS	480	420	450	480
False positives - not FH, cascaded	HIS	420	0	30	420
False negatives - FH, not cascaded	HIS	0	60	30	0
True negatives - FH, not cascaded	LIS[1]	100	520	490	100
RELATIVES*					
True positives - FH	HIS	765	1338	1385	1433
False positives - not FH cascaded	HIS	430	0	27	53
False negatives – FH not detected	LIS[2]	497	0	33	297
True negatives - not FH not cascaded	none	2611	1338	1513	2898
Total tested		**4302**	**2675**	**2959**	**4681**

HIS = High Intensity Statin; LIS[1] = all treated; LIS[2] = 1.3% treated (see assumptions)

1.8.1 Total costs of diagnosis for each strategy

The total costs of diagnosis include the total cost of clinical conformation for index cases, the cost of DNA testing for the index cases and the costs of contacting relatives and taking LDL-C measures (and DNA testing) for the diagnosis of relatives. The 100 referred patients classified as not having FH

were not cascaded from in any strategy, and would not be sent for DNA testing so costs for DNA includes only 900 patients. The total cost of clinical confirmation was estimated to be £282 per index case and £159 per relative. DNA testing was estimated to cost £400 per index case and £100 per relative. These costs were multiplied by the numbers of people tested under each strategy. The Cholesterol method is the cheapest strategy in making a diagnosis, with a cost of £965 per 1000 index cases entering the pathway, compared to the DNA methods which ranged between £1,334 to £1,653.

Table 9 Costs of diagnosis for the four strategies

	Cholesterol	**DNA**	**DNA+DFH**	**DNA+DFH+PFH**
INDEX CASES				
LDL-C measures	£282,140	£282,140	£282,140	£282,140
DNA testing	-	£360,000	£360,000	£360,000
Subtotal	***£282,140***	***£642,140***	***£642,140***	***£642,140***
RELATIVES				
LDL-C measures	£683,021	£424,720	£469,786	£743,144
DNA testing	-	£267,540	£267,540	£267,540
Subtotal	***£683,021***	***£692,260***	***£737,326***	***£1,010,684***
Total	**£965,161**	**£1,334,400**	**£1,379,466**	**£1,652,824**

1.8.2 Cost of treatment and QALY gain per patient estimated from the Markov model for both index cases and relatives

To estimate treatment costs and QALY gain from treatment for the different strategies, we modelled the discounted lifetime costs and benefits expected if subjects were given “high intensity” statin therapy compared to being on low intensity statins. All FH relatives identified as true FH cases detected were given high intensity statins. The low intensity statin was assumed to be simvastatin 40mg. Table 10, shows the cost per patient and QALY gain for patients on high intensity and low intensity statins for the index cases and relatives.

Table 10, Cost of treatment and QLY gain per patient

	Index Cases	
True FH (Index case)	Cost	QALYs
Low intensity treatment	£8,637	12.42
High intensity treatment	£13,586	12.70
Non FH (Index case)	Cost	QALYs
Low intensity treatment	£6,686	13.46
High intensity treatment	£13,052	13.53
	Relatives	
True FH (Relatives)	Cost	QALYs
Low intensity treatment	£18,440	12.76
High intensity treatment	£22,941	12.84
Non FH (Relatives)	Cost	QALYs
Low intensity treatment	£6,987	18.41
High intensity treatment	£15,021	18.50

The cost and QALY per person from treatment were used to estimate the total cost and QALY gain for each strategy under consideration, by multiplying the number of index cases recruited by the cost per and QALY gain per patient. For the relatives, a proportion (1.3%) (HSE 2003) 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%.

The total cost of each strategy was the sum of the diagnosis and treatment costs for each strategy. Table and Table below summarises the total cost of treatment and QALY gained by each strategy. Treatment costs accounted for the bulk of the costs. For instance, for the Cholesterol method diagnosis costs are about £1,000 per patient while the lifetime treatment costs are about £38,000 per patient.

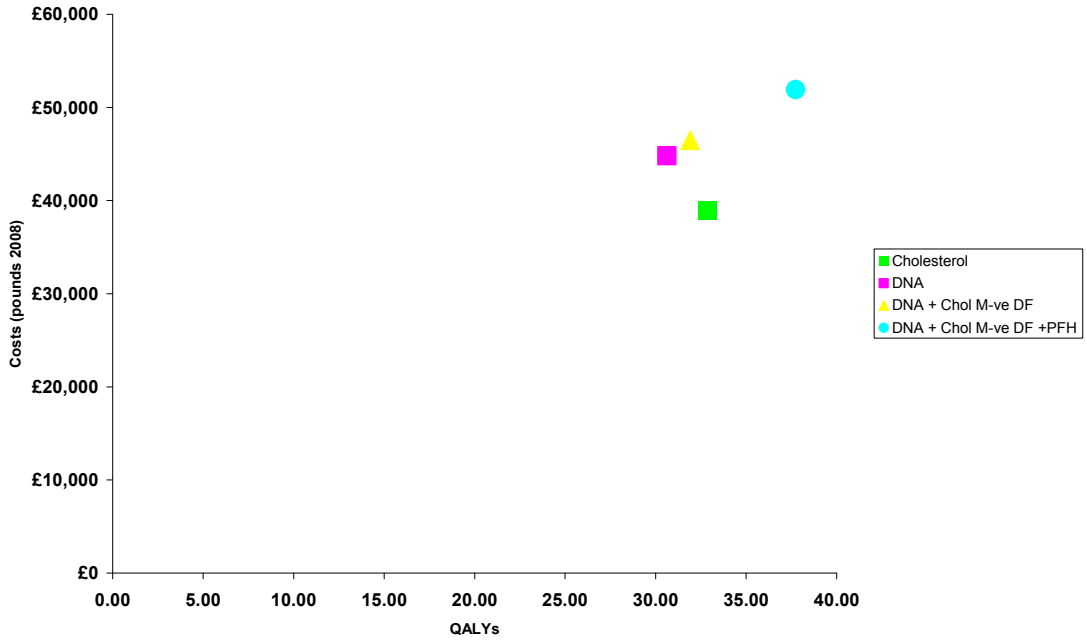
Table 11 Total cost of treatment for index cases and identified "affected" FH patients (costs in millions £)

TOTAL COST OF TREATMENT	Cholesterol	DNA	DNA + Chol M-ve DF	DNA + Chol M-ve DF +PFH
INDEX CASES				
True positives	£6.521	£5.706	£6.114	£6.527
False positives	£0.000	£0.815	£0.408	£0.000
False negatives - FH, low intensity statin	£5.482	£5.482	£5.482	£5.477
True negatives - not FH, low intensity statin	£0.669	£0.669	£0.669	£0.669
Subtotal	**£12.672**	**£12.672**	**£12.672**	**£12.672**
RELATIVES				
True positives	£17.539	£30.689	£31.785	£32.868
False positives	£0.039	£0.000	£0.002	£0.005
False negatives (FH, treated for lipids)	£7.470	£0.000	£0.503	£4.464
True negatives (no FH, treated for lipids)	£0.237	£0.122	£0.137	£0.263
Subtotal	**£25.284**	**£30.810**	**£32.427**	**£37.600**

Table 12 Total QALYs gained in each strategy

TOTAL QALYS GAINED FROM TREATMENT	Cholesterol	DNA	DNA + Chol M-ve DF	DNA + Chol M-ve DF +PFH
INDEX CASES				
True positives	6,095	5,333	5,714	6,100
False positives	0	762	381	0
False negatives - FH, treated for lipids	5,682	5,682	5,682	5,677
True negatives -not FH, treated for lipids	1,346	1,346	1,346	1,346
Subtotal	**13,123**	**13,123**	**13,123**	**13,122**
RELATIVES				
True positives	6,849	15,222	15,650	16,072
False positives	121	0	8	15
False negatives - FH, treated for lipids	7,530	0	508	4,600
True negatives -not FH, treated for lipids	598	316	356	681
Subtotal	**15,098**	**15,538**	**16,522**	**21,368**

Figure 1, Scatter plot showing the costs and effects of the different strategies under consideration



The scatter plot visually illustrates that the Cholesterol method is the cheapest of the four strategies. DNA and DNA + Chol M-ve DF are located to the left of the line joining cholesterol (green) and DNA + Chol M-ve DF +PFH (blue) hence are ruled out of the decision analysis by simple dominance. The relevant incremental comparison in this economic analysis is thus between the Cholesterol method (green box in the scatter plot) and the DNA + Chol M-ve DF +PFH (blue circle in the scatter plot)

Table 13, Base case results for the Incremental cost-effectiveness of the four strategies for cascade screening

Strategy	Cost (£)	Effect (QALYs)	Incremental cost (£)	Incremental effect QALY)	ICER (£/QALY)
Cholesterol	£38,921	32.87			
DNA	£44,816	30.63	-	-	**-**
DNA + Chol M-ve DF	£46,479	31.91	-	-	**-**
DNA + Chol M-ve DF +PFH	£51,924	37.73	£13,003	4.86	**£2,676**

The base case results are presented below, and cost-effectiveness is assessed against a threshold of £20,000/QALY. The table above shows the lifetime costs and QALY gains per patient by strategy. Cholesterol method dominates DNA alone and DNA + DF, that means Cholesterol method is cheaper and generates more QALYs compared to the two methods that it dominates. The model results indicate that the use of DNA testing plus cascading from both mutation negative definite FH individuals and individuals with possible FH is cost-effective when compared to the Cholesterol method. The estimated ICER is about £2,700/QALY.

Sensitivity analysis

A number of univariate sensitivity analyses were done by changing the base case assumptions. The model is very stable in sensitivity analysis, as the ICERs remained below £4,000/QALY when various assumptions were changed as shown in table 10 below.

1.8.2.1 Effect of age of index case and relatives on Incremental cost-effectiveness of the four strategies

Effect of age of index case and relatives on Incremental cost-effectiveness of the four strategies

In the base model, the starting age for the index case was 50 years, while for the relatives it was 30 years (representing the average age of the five first degree relatives of siblings and children). Assuming that index cases are diagnosed at 65 year of age and the relatives when they are over an average of 45 years, the cost-effectiveness conclusions were not affected. The estimated ICER fell to less than £2000 when the Cholesterol method was compared to DNA+DFH+PFH. Thus assumptions about the starting age of the index and the relatives do not affect the base case cost-effectiveness conclusion. This is expected as long as a strategy screens people who are eligible for treatment which improves clinical outcomes and the treatment

effect from the IDEAL and TNT which was used in the analysis was an average across all age groups.

1.8.2.2 Effect of treatment effect (using lower and upper 95%CI) on incremental cost-effectiveness of the four strategies

In the base model we used the point estimate of the meta-analysis of the IDEAL and TNT trials which compared high intensity compared with low intensity statins in people with stable coronary disease. In sensitivity analysis we used the lower and upper limit of the 95% confidence intervals. The model results are not sensitive to assumptions about treatment effect. The ICERs remained below £3,000/QALY when all outcomes were varied between lower and upper 95%CI.

1.8.2.3 Effect of different drug combinations and proportions of people on the different drugs on Incremental cost-effectiveness of the four strategies

The combination of drugs and proportions of people on the different drugs affects the overall price. The price of drugs was a weighted average of different combinations of drugs and the proportions of patients taking each drug. For the base model we used a combination that a GDG co-opted expert provided (Dr Antony Wiezbecki personal communication and reference provided). The drug costs were thus £389/year. In sensitivity analysis we used a combination used by the team updating the HTA FH Dr Dalya Marks personal communication). The annual drug costs were £484 (Dr Dalya Marks personal communication). The ICERs increased by just over £100 to £2,811/QALY, suggesting that the model results not sensitive to this assumption.

1.8.2.4 Other sensitivity analysis

Variables shown in Table 4 were changed by doubling or halving costs or time taken by health care professionals. In all cases changing the base

assumptions had minimal impact on the cost-effectiveness of the strategies. The table shows the ICERs, for DNA+DFH+PFH vs. Cholesterol method

For instance Table 4 shows that if assumptions about the number of relatives per index case was reduced from 5 to 3 for first degree and from 2 to 1 for second degree relatives, or was increased to 6 and 3 respectively, there is very little change in the cost per QALY. With fewer relatives per index cases, there is a slight increase in ICERs from £2,676 to £3,179/QALY and when there are more relatives per index case the ICERs fall to about £2,476/QALY. In the base model cascading was done to third degree relatives. We also assumed the cascading was stopped at second degree relatives and the ICERs slightly increased to £3,024/QALY. The cost of DNA testing was varied within the range suggested by the GDG between £200 and £600. Increasing the cost or halving them did not alter the base case conclusions. Percentage of index cases consenting to cascade testing in the base model were 65% and 60% for index and relatives respectively. In sensitivity analysis we used 85% & 80% for index and relatives which were that achieved by the FH audit team and further tested 100% consent for both index cases and relatives. The ICERs fell slightly in both cases.

We also modelled a fall in the price of statins. A reduction in the statin price of atorvastatin should follow the end of the patent period (after 2011), and we have estimated a 30% reduction in costs of all statins included in the model. This reduction resulted in a small effect on the ICERs. If the statin price were to fall by 30%, then the estimated ICERs will fall to £2,509 /QALY. We also changed the time taken by nurses, consultant, cost of sending letters, and percentage of relatives “false negatives treated with lower intensity statins in all cases this did not alter our cost-effectiveness conclusions. In the base model cascading was done to third degree relatives. The model is thus very stable in sensitivity analysis.

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Table 4 Other sensitivity analyses (which did not alter the base case conclusions)

	Cost/QALY Relevant comparison
Parameter	DNA+DFH+PFH vs. Cholest
BASE CASE RESULTS	**£2.676**
Percentage of index cases consenting to cascade testing 85% & 80%	£2,522
Percentage of relatives consenting to cascade testing 100%	£2,430
Double nurses time	£2,680
Halve nurses time	£2,673
Double consultant time	£2,681
Halve consultant time	£2,673
Costs of Cholesterol testing double	£2,677
Costs of Cholesterol testing halve	£2,675
Cost of letters double	£2,676
Cost of letters halve	£2,675
DNA £600 & £200	£2,768
DNA halve	£2,611
Cost of statins fall by 30%	£2,509
Limit cascading to second degree relatives	£3,024
Cascade from 3 first degree relatives and 1 second degree relatives	£3,179
Cascade from 6 first degree relatives and 3 second degree relatives	£2,476
Relative risk of non CVD death (RR=2)	£2,669
No discounting	£2,729
6% discount rate	£2,666
Index Age 65, relatives age 45	£1,215
Drug combinations (Dalya Marks's combination)	£2,811
Proportion of FN and TN relatives treated (0%)	£2,665
Proportion of FN and TN relatives treated (5%)	£2,705
Proportion of FN and TN relatives treated (100%)	£3,827
Using treatment effect from Simon Broome Register	£1,348
Treatment Effect varied across the 95% confidence interval	
Outcome	Lower 95% CI	Upper 95% CI
MI	£2,717	£2,638
stroke	£2,646	£2,717
TIA	£2,693	£2,661
PAD	£2,693	£2,661
Heart Failure	£2,682	£2,676
Rev	£2,612	£2,853
Unstable angina	£2,676	£2,664
CVD death	£2,607	£2,697

1.9 Discussion and conclusions

These analyses show that none of the strategies is ruled out by simple dominance. DNA + cascading from DFH mutation-negative index cases and DNA alone are ruled out by extended dominance. Thus the most cost-effective strategy is DNA testing plus cascading from both mutation negative definite FH individuals and individuals with possible FH is cost-effective when compared to Cholesterol method with an estimated ICER of £2,676/QALY.

It should be noted that in all the strategies modeled, it was 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 adequately treated with a lower dose of statin and the costs and benefits for this have been included in the model. We have assumed people over the age of 60 will benefit from statins to the same degree as the general population from statins. This is because the effectiveness data from the Simon Broome Register cohort show no significant reduction in mortality in FH patients over 60 years old[3]. We do not advocate ceasing drug treatment at the age of 60 years, but the cost-effectiveness of treating this patient group aggressively is less favorable. Our model did not include children, and due to a lack of effectiveness data, the consequences of screening and treating children have been omitted. 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 increases).

Our conclusions that DNA based methods are more cost-effective are consistent with other published studies. Marks (2002)[29] did a cost-effectiveness analysis from the NHS perspective which considered the different approaches to screening for FH patients aged between 16 and 54. They concluded that tracing of family members was the most cost-effective strategy with an estimated ICER of about £3097/LYG and universal

population screening was the least cost-effective strategy with an estimated ICER of £13,029/LYG. Marks (2003)[30] considered the costs and effects of different strategies for FH screening over a 10 year period. The authors again concluded that family tracing was the most efficient strategy and the cost per death averted was £3187. Wonderling (2004)[31] did a cost-effectiveness study of genetic screening programme in Netherlands FH patients compared to no screening. The cost per life-year gained was US$8 800. The result was sensitive to the price of statin treatment and the number of life-years gained.

The modeling supports cascade testing using a combination of both DNA information and LDL-C levels where a mutation has not been identified based on an initial group of index patients with a strong clinical suspicion of FH. Although a number of assumptions were necessary, sensitivity analysis indicates that changes in the response rate, costs of nurses and consultant time, or costs of lipid or of DNA testing have a negligible impact on the overall conclusions.

The majority of the costs involved are for treatment. However, the model results are insensitive to the cost of statins. Due to the genetic nature of the defect in patients with FH, patients will frequently require either a high dose of one of the more efficacious statins or a combination of several different lipid lowering drugs to achieve adequate LDL-C lowering. Because FH patients have very high LDL cholesterol levels from birth, this warrants the use of high intensity lipid lowering therapy sufficient to reduce LDL-cholesterol to recommended levels, and longitudinal cohort studies have shown that statin treatment is associated with reduced mortality[3]. In our model we have used a combination of statins and the model was not sensitive to this assumption.

One of the most important consequences of cascade testing where DNA information is not available is the high false-positive and false-negative rate for the identification of affected and non-affected relatives based on LDL-C measurements. An overlap between LDL-C levels in FH and non FH children is well established[32],[33] and false-positive and false-negative rates of between

8-15% for families followed up through DNA testing and subsequent lipid measurements have been observed in a number of different studies. The data used here for the false-positive and negative rates for LDL-C measures was obtained from an analysis of the Dutch relative dataset of more than 2000 mutation carriers and 4000 non-mutation carrying relatives, which represents the largest data set available[24]. However when this is analyzed by age cut-offs, some of the groups have small numbers which reduces accuracy, and there is also uncertainty as to the direct applicability of cut-offs based on patients in the Netherlands to patients in the UK. This data do however represent the best information available.

While a false-negative diagnosis may deny a 'true FH' patient and possibly their offspring (who are at 50% risk of inheriting the mutation) the benefit of more intensive lipid-lowering therapy for their specific condition, another significant issue is that cascade testing from false-negative people (i.e. relatives who have elevated LDL-C levels who do not carry the family mutation) will not result in any true FH patients being identified. UK data characterising LDL-C levels in mutation-carrying and non-carrying relatives are needed so that the most appropriate cut-offs can be obtained so that cascade testing from non-mutation FH index cases can be carried out with optimal efficiency.

It is anticipated that the proportion of definite FH patients in whom a mutation can be identified is likely to increase over the next few years. This will both be because of improvements in the current techniques for mutation identification, and also the identification of new genes where mutations cause FH. Such improvements will increase the cost-effectiveness of the strategy as people will be correctly identified as needing the necessary treatment and for secondary cascading

.

In conclusion, using a threshold of £20,000/QALY, the most cost-effective method for cascade screening is strategy using DNA testing plus cascading

from both DFH and PFH mutation negative index cases compared to the Cholesterol method. DNA alone and DNA + cascading from DFH mutation negative index cases are ruled out by simple dominance. The model results are stable in sensitivity analysis.

Data tables and figures

1.10 Data tables

Table 1, Distribution of primary CVD events without taking statins in general population

Age	Unstable Angina	Revascularisation	MI	PAD	Heart Failure	TIA	Stroke	CVD death
30	11.20%	7.88%	18.75%	7.50%	0.25%	11.0%	17.00%	9.60%
50	9.20%	6.88%	15.98%	10.50%	1.15%	10.1%	21.30%	10.80%
65	6.75%	9.00%	14.70%	15.50%	4.05%	8.9%	42.60%	16.55%
75	5.75%	3.50%	13.15%	25.50%	10.43%	8.9%	40.35%	14.75%
85	6.25%	0.63%	14.30%	57.00%	10.43%	5.2%	42.60%	14.20%

For unstable angina, MI, stroke, and CVD death: Ward et al 2005[6] ScHARR statins model, ttp://www.nice.org.uk/pdf/statins_assessment_report.pdf.

For heart failure Cowie MR,[34] For PAD: Murabito JM[35] For revascularisation: Johansen H[36].

Table 2, Annual baseline probability of primary CVD events for true FH index patients taking low intensity statins with no-prior CVD

Age	Unstable Angina	Revascularisation	MI	PAD	Heart Failure	TIA	Stroke	CVD death
30	18.88%	13.28%	31.61%	0.15%	0.42%	0.17%	0.34%	16.19%
50	1.24%	0.93%	2.16%	0.25%	0.16%	0.24%	0.51%	1.46%
65	0.21%	0.28%	0.45%	0.40%	0.12%	0.23%	1.09%	0.51%
75	0.19%	0.12%	0.44%	0.70%	0.35%	0.25%	1.11%	0.49%
85	0.22%	0.02%	0.51%	1.68%	0.37%	0.15%	1.26%	0.50%

Table 3, Annual baseline probability of primary CVD events for false positive FH index patients taking low intensity statins with no-prior CVD

Age	Unstable Angina	Revascularisation	MI	PAD	Heart Failure	TIA	Stroke	CVD death
30	0.27%	0.19%	0.45%	0.15%	0.01%	0.220%	0.340%	0.23%
50	0.26%	0.20%	0.46%	0.25%	0.03%	0.240%	0.507%	0.31%
65	0.21%	0.28%	0.45%	0.40%	0.12%	0.227%	1.095%	0.51%
75	0.19%	0.12%	0.44%	0.70%	0.35%	0.246%	1.114%	0.49%
85	0.22%	0.02%	0.51%	1.68%	0.37%	0.152%	1.257%	0.50%

Table 4, Annual baseline probability of primary CVD events for true FH relatives taking low intensity statins with no-prior CVD

Age	Unstable Angina	Revascularisation	MI	PAD	Heart Failure	TIA	Stroke	CVD death
30	14.16%	9.96%	23.71%	0.11%	0.32%	0.17%	0.26%	12.14%
50	0.98%	0.73%	1.70%	0.20%	0.12%	0.19%	0.40%	1.15%

65	0.17%	0.22%	0.37%	0.32%	0.10%	0.18%	0.88%	0.41%
75	0.16%	0.09%	0.36%	0.58%	0.28%	0.20%	0.91%	0.40%
85	0.17%	0.02%	0.39%	1.29%	0.28%	0.12%	0.96%	0.39%

Table 5, Annual baseline probability of primary CVD events for false positives relatives taking low intensity statins with no-prior CVD

Age	Unstable Angina	Revascularisation	MI	PAD	Heart Failure	TIA	Stroke	CVD death
30	0.20%	0.14%	0.34%	0.11%	0.00%	0.165%	0.255%	0.17%
50	0.21%	0.16%	0.36%	0.20%	0.03%	0.152%	0.320%	0.24%
65	0.17%	0.22%	0.37%	0.32%	0.10%	0.133%	0.639%	0.41%
75	0.16%	0.09%	0.36%	0.58%	0.28%	0.134%	0.605%	0.40%
85	0.17%	0.02%	0.39%	1.29%	0.28%	0.077%	0.639%	0.39%

Table 6, Deaths by age, sex and underlying cause, 2004 registrations, England and Wales in the general population

Deaths by age, sex and underlying cause, 2004 registrations, England and Wales

	DEATHS								
	All cause ICD10: A00-R99			Circulatory ICD: I00-I99			Proportion of non-circulatory deaths to all deaths		
	M	F	ALL	M	F	ALL	M	F	ALL
45	12,417	8,139	20,556	3,930	1,362	5,292	68%	83%	74%
55	27,117	17,649	44,766	9,330	3,541	12,871	66%	80%	71%
65	52,709	37,041	89,750	19,783	11,304	31,087	62%	69%	65%
75	87,367	88,404	175,771	35,607	35,958	71,565	59%	59%	59%
85	51,329	109,488	160,817	20,816	46,470	67,286	59%	58%	58%

Source: GAD

Table 7, estimated non-CVD death rates used in the model

	All cause *	Non-CVD
45	0.35%	0.26%
55	0.88%	0.63%
65	2.37%	1.55%
75	6.75%	4.00%
85	36.29%	21.11%

Table 8 Baseline input parameters from different health states (annual transition probabilities)

Age	30	50	65	75	85
From FH no prior CVD event to					
MI	0.316	0.022	0.005	0.004	0.005
Stroke	0.003	0.005	0.011	0.011	0.013
peripheral artery disease	0.002	0.002	0.004	0.007	0.017

heart failure	0.004	0.002	0.001	0.003	0.004
revascularisations	0.133	0.009	0.003	0.001	0.000
unstable angina	0.189	0.012	0.002	0.002	0.002
cardiovascular death	0.162	0.015	0.005	0.005	0.005
From MI to					
MI	0.022	0.022	0.027	0.039	0.039
Stroke	0.007	0.008	0.012	0.023	0.023
heart failure	0.012	0.012	0.012	0.012	0.012
revascularisations	0.067	0.067	0.067	0.067	0.067
unstable angina	0.021	0.021	0.021	0.021	0.021
cardiovascular death	0.005	0.007	0.015	0.030	0.030
From Stroke to					
Stroke	0.077	0.167	0.207	0.263	0.333
MI	0.002	0.167	0.006	0.008	0.010
heart failure	0.005	0.005	0.005	0.005	0.005
revascularisations	0.000	0.000	0.000	0.000	0.000
unstable angina	0.006	0.006	0.006	0.006	0.006
cardiovascular death	0.005	0.011	0.026	0.059	0.122
From peripheral artery disease to					
MI	0.016	0.016	0.016	0.016	0.016
Stroke	0.016	0.016	0.016	0.016	0.016
cardiovascular death	0.082	0.082	0.082	0.082	0.082
From Heart failure to					
heart failure	0.042	0.042	0.042	0.042	0.042
MI	0.008	0.008	0.008	0.008	0.008
Stroke	0.002	0.002	0.002	0.002	0.002
revascularisations	0.000	0.000	0.000	0.000	0.000
unstable angina	0.008	0.008	0.008	0.008	0.008
cardiovascular death	0.045	0.045	0.045	0.045	0.045
From revascularisations to					
revascularisations	0.039	0.039	0.039	0.039	0.039
MI	0.030	0.030	0.030	0.030	0.030
Stroke	0.010	0.010	0.010	0.010	0.010
heart failure	0.015	0.015	0.015	0.015	0.015
cardiovascular death	0.006	0.006	0.006	0.006	0.006
Unstable angina to					
revascularisations	0.142	0.142	0.142	0.142	0.142
MI	0.049	0.049	0.049	0.049	0.049
Stroke	0.014	0.014	0.014	0.014	0.014
heart failure	0.044	0.044	0.044	0.044	0.044
cardiovascular death	0.005	0.005	0.005	0.005	0.005

Table 9 Treatment effect of statins, results of meta-analysis of IDEAL[10] & TNT[9] for patients with stable coronary artery disease

Outcome	Mean	Lower 95%ci	Upper 95%ci
MI	0.81	0.72	0.91
stroke	0.82	0.70	0.96
TIA	0.79	0.65	0.94
PAD	0.87	0.69	1.00
Heart Failure	0.77	0.65	0.92
Rev	0.78	0.69	1.00
Unstable angina	0.84	0.71	0.86
CVD death	0.92	0.72	1.00
Death other	1.00	1.00	1.00

Table 10 Treatment effect of statins, results from the updated Simon Broome Register[7] for patients with FH

AGE	Mean	Lower limit 95% CI	Upper limit 95% CI
<40 YRS	0.13	0.1	0.18
40-59YRS	0.52	0.45	0.6
>60YRS	0.82	0.75	0.9

Table 11, Costs of CVD events

Health state	Mean	Lower	Upper	Source
Well	£68	£52	£80	GDG assumption
MI (first year)	£1,291	£804	£1,986	NHS ref cost 2007
MI (subsequent)	£500	£200	£650	NICE CG 34 2006
Stroke (first year)	£8,046	£5,886	£11,539	NICE TA 94
Stroke (subsequent)	£2,163	£1,100	£3,000	NICE TA 94
PAD (first year)	£1,000	£612	£1,388	Karnon 2005
PAD (subsequent)	£264	£200	£400	Assumption same as TIA
Heart failure	£2,303	£1,255	£3,434	NHS ref cost 2007
Heart failure (subsequent)	£500	£200	£650	Assumed same as post MI
Revasc	£10,456	£8,012	£11,925	NHS ref cost 2007
Revasc (subsequent)	£500	£200	£650	Assumed same as post MI
Unstable angina (first year)	£1,059	£448	£1,521	NHS ref cost 2007
Unstable angina (subsequent)	£500	£200	£600	Assumed same as post MI

Table 12 Annual drug costs taken from the Prescription Pricing Division March 2008

Drug	Number of tablets	Cost/packet	Cost/year
Simvastatin 40mg	28	£1.39	£18.12
Simvastatin 40mg	28	£4.95	£64.53
Atorvastatin 80mg	28	£28.21	£367.74
Simvastatin 40mg + ezetimibe	28	£33.42	£435.65
Simvastatin 80mg + ezetimibe	28	£41.21	£537.20
Ezetimibe	28	£26.21	£341.67

Source: Drug Tariff March 2008[13]

Table 13 Unit costs of health care professionals and estimated times taken in hours to attend to patients

HCP	Unit cost/hr	Time Hrs(IC)	Time Hrs(Rel)	Cost Index	Cost Relatives	Source
Nurse	£58.00	2	1	£116.00	£58.00	[26]
Clerk	£15.00	1	0.5	£15.00	£7.50	ibid
Phlebotomy	£15.00	0.17	0.17	£2.55	£2.55	ibid
Consultant	£175.00	0.75	0.42	£131.25	£73.50	ibid
Non-fasting TC	£7.00			£7.00	£7.00	Dr Dalya Marks (personal communication)
Full, fasting TC	£8.00			£8.00	£8.00	ibid
£ letter for relatives	£0.86			£0.00	£0.86	ibid
Cost of GP visit	£34/visit lasting 11.7 minutes					[26]

Table 14 Proportions of patients on different Lipid-lowering drugs estimated from Wald et al used for the base model, data provided by Dr Anthony Wierzbicki, personal communication

Drug	% (proportions on the drug)*
Simvastatin 40mg	2%
Simvastatin 80mg	9%
Atorvastatin 80mg	64%
Simvastatin 40mg + ezetimibe	4%
Simvastatin 80mg + ezetimibe	11%
Atorvastatin 40mg + ezetimibe	10%

Table 15 Proportions of patients on different Lipid-lowering drugs data provided by Dr Dalya Marks (personal communication)

Drug	% (proportions on the drug)*
Atorvastatin 40mg	30%
Atorvastatin 40mg + ezetimibe	30%
Atorvastatin 80mg	10%
Atorvastatin 80mg + ezetimibe	10%
Simvastatin 40mg	5%
Simvastatin 40mg+ ezetimibe	5%
Simvastatin 80mg	5%
Simvastatin 80mg+ ezetimibe	5%

Table 16, Health state utilities

Health State	Mean	Lower limit	Upper limit	Source
Well	0.95	0.9	1	Chen 2001
MI	0.76	0.56	0.96	NICE TA 94
Post MI	0.88	0.76	1.00	Mason J 2005
Stroke	0.63	0.43	0.83	NICE TA 94
Post stroke	0.63	0.43	0.83	NICE TA 94
PAD	0.90	0.86	0.98	Karnon 2005
Post PAD	0.90	0.86	0.98	assumption
Hear failure	0.68	0.48	0.88	Davies 2006
Post Heart failure	0.68	0.48	0.88	assumption
Revascu	0.93	0.74	1.00	Yorck 2003
Post revascu	0.93	0.74	1.00	assumption
Unstable angina	0.77	0.57	0.97	NICE TA 94
Post unstable angina	0.88	0.60	1.00	assumed same as post MI

Table 17, Age-related utility from Health Survey for England 1996

Age specific quality of life

Age group	Mean	SE
45-54	0.85	0.004
55-64	0.79	0.006
65-74	0.78	0.006
75+	0.73	0.007

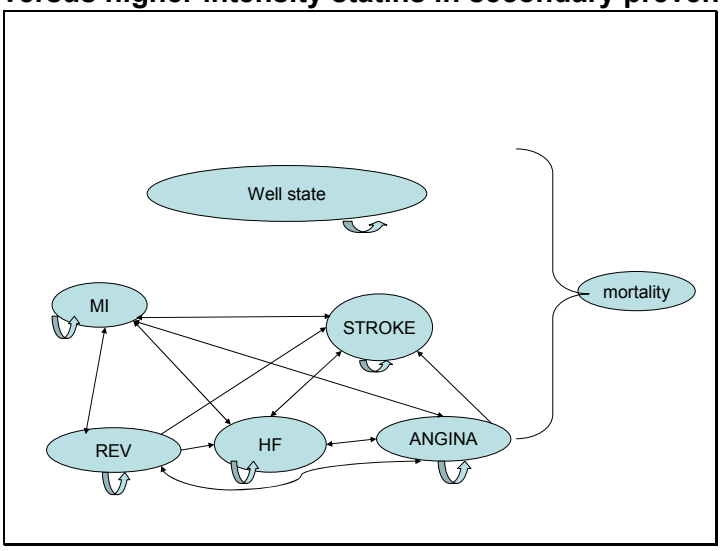
Source: Health survey of England 1996

Table 18 Decision tree probabilities for the cascade model

	Probability	Source
Prevalence of DFH using Simon Broome	0.3	Simon Broome
Prevalence of PFH using Simon Broome	0.6	Simon Broome
Prevalence of no FH using Simon Broome	0.1	Simon Broome
Probability of true FH for a DFH using Cholesterol method	0.9	The UK FH Cascade Audit Project (FHCAP) Personal communication from Dr G Hadfield + GDG
Probability of true FH for a PFH using Cholesterol method	0.35	Ibid
Probability of mutation positive for a DFH using DNA method	0.8	Ibid
Probability of mutation positive for a PFH using DNA method	0.3	Ibid
		Ibid
Probability of true FH for a DFH mutation negative using Cholesterol method	0.5	Ibid
Probability of true FH for a PFH mutation negative using Cholesterol method	0.07	Ibid
Cascading probabilities		
From index cases true positives		
Probability of true positives using Cholesterol method	0.32	Starr et al 2008 (In press)
Probability of false positives using Cholesterol method	0.08	Ibid
Probability of true negatives using Cholesterol method	0.42	Ibid
Probability of false negatives using Cholesterol method	0.18	Ibid
From index cases false positives		
Probability of true positives using Cholesterol method	0	Ibid
Probability of false positives using Cholesterol method	0.16	Ibid
Probability of true negatives using Cholesterol method	0.84	Ibid
Probability of false negatives using Cholesterol method	0	Ibid

1.11 Figures

Figure 1 Model structure for cost-effectiveness of lower intensity statins versus higher intensity statins in secondary prevention



Review: FH meta-analysis
Comparison: 09 Total mortality
Outcome: 01 Total

Study or sub-category	Favors high dose n/N	Favors low dose n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
IDEAL	366/4439	374/4449		57.36	0.98 [0.85, 1.13]
TNT	284/4995	282/5006		42.64	1.01 [0.86, 1.18]
Total (95% CI)	9434	9455		100.00	0.99 [0.89, 1.10]

Total events: 650 (Favors high dose), 656 (Favors low dose)
Test for heterogeneity: Chi² = 0.07, df = 1 (P = 0.79), I² = 0%
Test for overall effect: Z = 0.13 (P = 0.89)

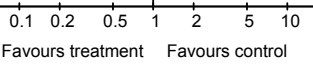
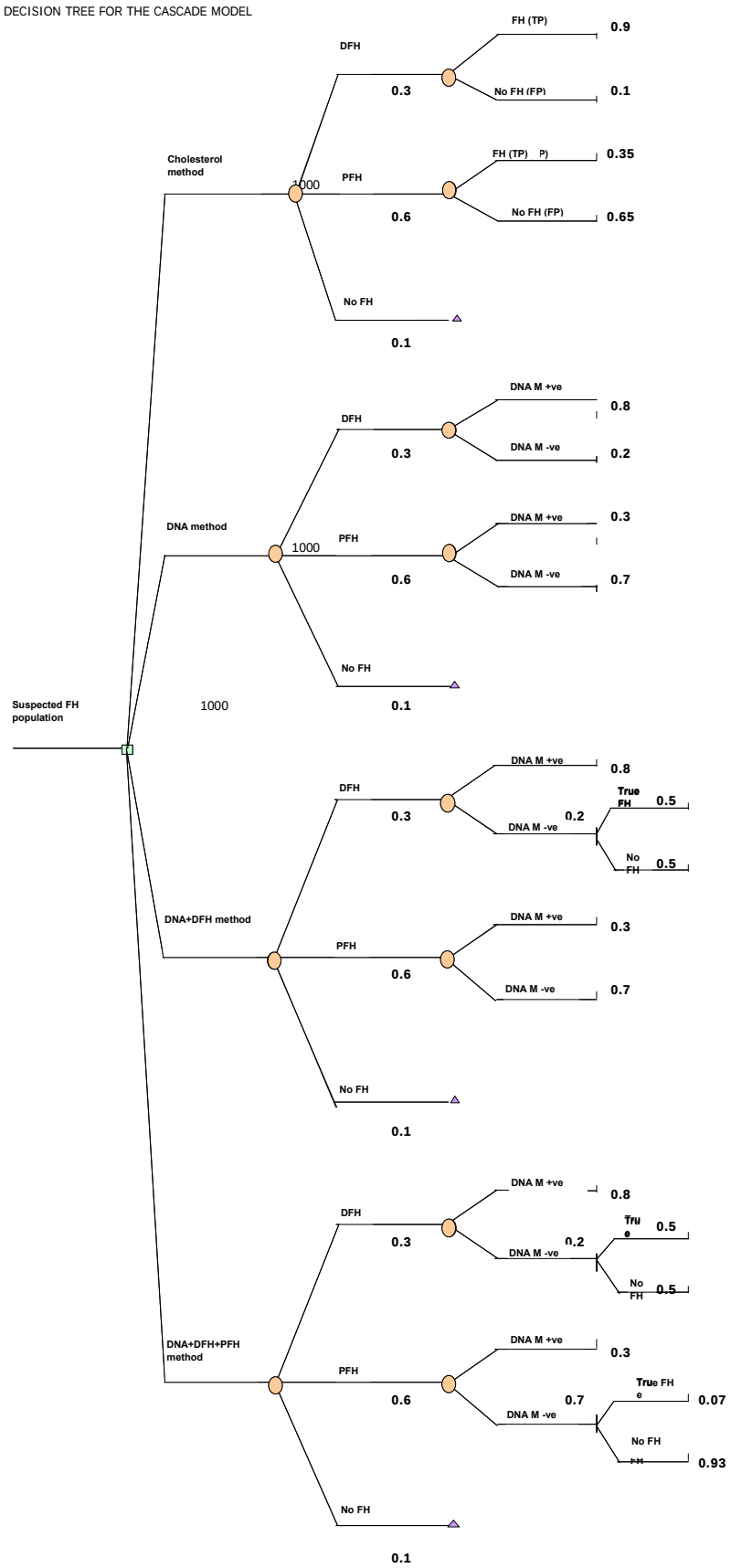


Figure 2 Decision model for cascade screening



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