# Cost-utility analysis of searching electronic health records and cascade testing to identify and diagnose familial hypercholesterolaemia in England and Wales

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## Abstract

**Objective:** The cost effectiveness of cascade testing for familial hypercholesterolaemia (FH) is well recognised. Less clear is the cost effectiveness of FH screening when it includes case identification strategies that incorporate routinely available data from primary and secondary care electronic health records.
**Methods:** Nine strategies were compared, all using cascade testing in combination with different index case approaches (primary care identification, secondary care identification, and clinical assessment using the Simon Broome (SB) or Dutch Lipid Clinic Network (DLCN) criteria). A decision

analytic model was developed consisting of a decision tree and Markov state-transition models. It was informed by three systematic literature reviews, meta-analysis of diagnostic test accuracy, and expert advice provided by a NICE Guideline Committee.
**Results:** The model confirmed the results of other studies that cascade testing is a cost-effective strategy. The addition of primary care case identification by database search for patients with recorded cholesterol values above the 99.5$^{th}$ percentile of the population was more cost effective than cascade testing alone. The incremental cost-effectiveness ratio (ICER) of clinical assessment using the DLCN criteria was £3,254 per quality-adjusted life year (QALY) compared with case-finding with no genetic testing. The ICER of clinical assessment using the SB criteria was £13,365 per QALY (compared with primary care identification using the DLCN criteria), indicating that the SB criteria was preferred because it achieved additional health benefits at an acceptable cost. Secondary care identification with either the SB or DLCN criteria, was not cost effective, alone (dominated and dominated respectively) or combined with primary care identification (£63, 514 per QALY, and £82,388 per QALY respectively).
**Conclusions:** Searching primary care databases for people at high risk of FH followed by cascade testing is likely to be cost-effective. The combined possible and definite SB criteria is slightly more cost effective than the standard DLCN criteria.

## Introduction

Familial hypercholesterolaemia (FH) is characterised by an inherited genetic mutation which causes a high cholesterol concentration from birth. People with FH have a higher risk of coronary heart disease (CHD), particularly at younger ages.[1] Once diagnosed, lifestyle changes and lipid modification treatment substantially reduce the risk of CHD.[2 3]

It is estimated that between 115,000 and 267,000 people in England and Wales have FH but only 18,000 are currently diagnosed, representing an opportunity to substantially reduce the mortality and morbidity associated with the disease.[1 4 5] Cascade testing is recommended by clinical guidelines to identify people with FH who are currently undiagnosed because it has been shown to be effective and cost effective.[6-9] Cascade testing is the process of inviting relatives of people currently diagnosed with FH to undergo genetic testing to see if they carry the family mutation. However, it has been estimated that only half of all carriers are likely to be identified using this strategy.[5]

New evidence has emerged on the effectiveness of searching primary care and secondary care databases for people at high risk of FH based on routinely collected information on biochemical tests, clinical signs including xanthomas, personal history of cardiovascular disease (CVD) and family medical history.[10-16] Examples of biological markers are high LDL-cholesterol (LDL-C) and high total cholesterol. Other characteristics may include a family history of early CHD. Based on these characteristics, the clinician may assess the patient against standard FH diagnostic criteria, usually the Simon Broome (SB) or Dutch Lipid Clinic Network (DLCN) criteria. Those identified with possible FH would be referred to a lipid clinic for specialist consultation and genetic testing.

The cost effectiveness of searching databases should be established prior to wider adoption because of the resource impact on healthcare providers and the National Health Service (NHS). Activities that require resource reallocation include informatics setup, training staff in GP surgeries, contacting patients to invite them for further assessment, lipid clinic consultations, genetic testing and

treatment following a positive diagnosis. Whether this resource impact is cost effective is influenced by the likelihood people identified for further assessment actually have FH, the diagnostic accuracy of the diagnostic criteria, the take up rates of clinical assessment and cascade testing, and the costs and health benefits associated with long term lipid modification treatment.

Recommendations in the original NICE guideline were based on economic modelling of cascade testing only conducted by Nherera et al. in 2011.[6] The 2017 update identified studies supporting the cost effectiveness of cascade testing but revealed that the cost effectiveness of new index case identification in primary care or secondary care had not been investigated.[6-9 17] The present economic analysis was developed to provide this evidence.

## Methods

### Population and subgroups

There are six groups of people that have the potential to come in to contact with the interventions: current index cases, potential new index cases from primary or secondary care, and the relatives of people in each of these three groups.

Current and potential new index cases, consisting of the groups of people with a current clinical diagnosis, people identified in a primary care database as requiring further investigation, and people identified in a secondary care database as requiring further investigation, were further stratified to differentiate people that had a monogenic cause of their hypercholesterolaemia (autosomal dominant FH caused by mutations in the *LDLR*, *APOB* and *PCSK9* genes) and those with multifactorial hypercholesterolaemia. Within the multifactorial group will be individuals with a polygenic aetiology due to co-inheritance of common LDL-C-raising variants ("polygenic hypercholesterolaemia").[18 19] Genetically confirmed monogenic FH is associated with a greater risk of CHD compared with polygenic hypercholesterolaemia.[20 21] For the purposes of modelling, a simplifying assumption was made that relatives cannot carry both monogenic FH and polygenic hypercholesterolaemia. Long term modelling was conducted including cohorts of males and females beginning between age 40 and 70 that were broadly representative of the UK population within these age bands.

### Strategies compared

The strategies that were compared in the analysis are summarised in Table 1. The diagnostic pathway and resource use associated with each strategy was mapped in consultation with the NICE Guideline Committee.[17] The full description of each strategy along with diagrams in the form of a decision tree are provided in the Supplementary Material.

**Table 1: Characteristics of strategies compared in the analysis**

| Strategy | Genetic cascade testing | Search primary care database | Search secondary care database | SB criteria for clinical assessment (base case possible & definite) | DLCN criteria for clinical assessment (base case score > 5) |
|---|---|---|---|---|---|
| Strategy 1 | ✘ | ✘ | ✘ | ✘ | ✘ |

| | | | | | |
|---|---|---|---|---|---|
| Strategy 2 | ✓ | ✘ | ✘ | ✘ | ✘ |
| Strategy 3 | ✓ | ✓ | ✘ | ✓ | ✘ |
| Strategy 4 | ✓ | ✓ | ✘ | ✘ | ✓ |
| Strategy 5 | ✓ | ✘ | ✓ | ✓ | ✘ |
| Strategy 6 | ✓ | ✘ | ✓ | ✘ | ✓ |
| Strategy 7 | ✓ | ✓ | ✓ | ✓ | ✘ |
| Strategy 8 | ✓ | ✓ | ✓ | ✘ | ✓ |
| Strategy 9 | ✓* | ✓ | ✘ | ✘ | ✘ |

SB: Simon Broome; DLCN: Dutch Lipid Clinic Network

* Cascade testing offered to the relatives of currently diagnosed index cases only.

The NICE guideline committee selected the SB and DLCN criteria as the most widely used clinical assessment tools out of nine available.[22] Onward referral for genetic testing is typically considered when a patient has 'possible' or 'definite' FH on the SB criteria or a score greater than 5 on the DLCN criteria.[1] Genetic testing is the gold standard for diagnosing monogenic FH.

## Modelling approach

The setting of interest is the NHS in England and Wales. Costs were derived using the perspective of the NHS and include direct medical costs, such as the staff cost of searching databases, conducting clinical assessment in primary or secondary care settings and genetic testing. The perspectives of people with FH and multifactorial hypercholesterolaemia were adopted for health benefits. A lifetime time horizon was adopted. Both costs and health outcomes were discounted at an annual rate of 3.5% as specified by NICE.

The structure of the model consisted of five modules. The first was a decision tree capturing short term identification, diagnosis and cost outcomes. Short term outcomes included the proportion of people with FH who were treated vs. untreated and the cost of searching electronic health records, clinical assessment and genetic testing. The four remaining modules were Markov traces that captured long term consequences. People were assigned to the 'Untreated FH' module if they were incorrectly diagnosed as not having FH (false negatives) or because they were not identified, as there was no opportunity to within that strategy. This module was adapted from the cost-effectiveness analysis of statin treatment for the primary and secondary prevention of cardiovascular disease in NICE CG181. This model had eight alive health states plus seven transition states and was adjusted to account for the different risk profile of people with FH. People were assigned to the 'Treated FH' module if they were correctly identified and diagnosed with FH. Costs and treatment effect were based on atorvastatin 80mg. People with polygenic hypercholesterolaemia were assigned to the 'Untreated polygenic' module if they did not come in to contact with a health care professional as part of the intervention and health outcomes were identical to the CG181 model. If people with polygenic hypercholesterolaemia were already on statins prior to intervention or came in to contact with health care they were assigned to the 'Treated polygenic' module. A simplifying assumption was made that all people in this module were treated with atorvastatin 20mg although it is recognised that, in practice, people with polygenic hypercholesterolaemia will be prescribed this treatment only if their QRISK is >10%. Costs were updated to the most recent financial year for which reference costs were available, 2015-16. Probabilistic sensitivity analysis (PSA) was conducted to enable an assessment of the joint uncertainty in the results and to calculate the probability that each intervention was cost effective.

## Outcomes

The short term module reported the number and proportion of people with FH and polygenic hypercholesterolaemia who were treated vs. untreated. It also calculated short term diagnostic outcomes of interest, such as the number of genetic tests conducted as a result of false positive clinical assessments and the total short term economic cost by subpopulation. Long term costs and quality-adjusted life years (QALYs) were then included in the overall assessment of cost-effectiveness.

## Input parameters

The key input parameters are provided in the Supplementary Material and briefly summarised below.

The number of people with a current clinical diagnosis of FH was informed by an audit of lipid clinics in the UK in 2010.[5] The proportion of people with a current clinical diagnosis that actually had a functional mutation in the *LDLR*, *APOB* or *PSK9PSK9* gene was taken from the experience of the Welsh, Scottish and Wessex FH services.[9] A conservative estimate of 1/500 was used for the prevalence of FH in the general population.[1] This was varied up to 1/217 in sensitivity analysis.[4] The size of the adult population of England and Wales was used to represent the number of people registered in primary care databases and sourced from the Office of National Statistics.

The availability of relevant cholesterol data was estimated at 31% in the UK context.[10 23] This value affects the overall resource impact but not the cost-effectiveness of primary care case finding as there are few fixed costs within the model. The take up of clinical assessment by people identified by a primary care database search was informed by the general practice and workplace identification cohorts of an Australian study.[14] The prevalence of FH in people with early myocardial infarction (MI) was informed by a UK study of people genetically tested for *LDLR* gene deletions or duplications.[24] In sensitivity analysis, this was varied between the lower 95% confidence interval from the same study up to an alternative mean estimate from a study based on clinical assessment to diagnose FH in the secondary care setting.[24 25] The take up of clinical assessment and genetic testing by people with early MI was informed by the UK study of genetically-confirmed prevalence and varied by +/-25% in sensitivity analysis.[24] The prevalence of people with early MI was sourced from a summary of the epidemiology of cardiovascular disease in the UK.[26] The number of relatives invited for cascade testing per index case was estimated from a finding that 1.33 relatives were genetically tested per index case in the Scottish, Welsh and Wessex FH services and that 59.89% relatives take up cascade testing (1.33/0.5989 = 2.22).[9 27] This parameter was varied in sensitivity analysis between 1 relative, based on a worst-case scenario, and 12 relatives, based on an optimistic assumption used in a previous NICE costing report from 2009. The accuracy of the SB and DLCN diagnostic criteria was established through systematic review and meta-analysis.

In the base case a more inclusive 'rule out' profile was used for referral to a lipid clinic and genetic testing: possible or definite according to the SB criteria and a score >5 for the DLCN criteria because sensitivity was prioritised over specificity by the NICE guideline committee. Sensitivity analysis using the 'definite' only criteria for each tool was also examined.

The increased risk of CHD due to FH was based on data from the Simon Broome register (personal communication, S. Humphries).[3] The *relative* treatment effect of lipid modification on CVD risk was

assumed to be the same in the FH population as in the general population due to a lack of evidence on the adult FH population identified in the systematic review conducted for the 2017 update to the NICE guideline. Placebo-controlled trials have not included people with FH because it is unethical to withhold treatment from patients with severe hypercholesterolaemia due to high lifetime risk of CHD. Appropriate treatment with statins was assumed to result in the same *relative* reduction in CVD event risk whether that was achieved with statins or ezetimibe or a combination of both in the base case. A recent study of a Spanish cohort suggested that the base case risks of CHD events may have been too high.[28] A sensitivity analysis was conducted in which the model outputs for patients with treated FH were calibrated to match the outcomes observed in this trial.

**Costs**

The cost of genetic testing was obtained from the UK Genetic Testing Network. Several laboratories offer FH testing services throughout England and Wales and the median cost was used in the base case. The highest and lowest costs were used in sensitivity analysis. Staff costs were obtained from the Personal Social Services Research Unit's report of unit costs in the NHS.[29] Itemised resource use used to calculate healthcare and admin staff inputs associated with genetic testing were obtained from a recent cost-utility analysis of genetic cascade screening.[9]

## Results

### Short term results

Under the base case settings of the model, the maximum number of people with FH that were able to be diagnosed (at 100% take up, sensitivity and specificity) was 43,961 (Figure 1). This assumed a data availability rate of 31% in primary care, which crucially determined the number of people that are able to be found by the case finding strategies. This figure was also based on the number of relatives approached for cascade testing, set at 2 in the base case.

Strategy 2, cascade testing only, resulted in 2,354 relatives being diagnosed and treated, increasing the proportion of people with FH in the model who were treated from 19% to 25%. Strategy 3 and Strategy 4, primary care case identification with the SB and DLCN criteria respectively, had very similar results with approximately 6,100 new FH index case diagnoses in addition to over 2,000 new diagnoses resulting from cascade testing the relatives of the new index cases. This increases to 37% the people with FH in the model being identified. Due to the relatively small numbers of people with early MI, secondary care case identification strategies identified close to 600 relatives of new index cases with FH. The strategy that diagnosed the most number of people with FH was Strategy 7, primary and secondary care case identification with clinical assessment using the SB criteria.

Total short term economic cost was calculated for each strategy by setting (Table 2). These figures take account of the opportunity cost of a consultation taken up for clinical diagnosis, rather than additional resource on staff costs in general practice. This analysis found that most of the short term cost of the strategies is borne by secondary care and genetic testing services. Apart from Strategy 1 (no intervention), the lowest short term economic cost was £11 million for Strategy 2 (cascade testing only) and the highest was £58 million for Strategy 7, case identification in both primary and secondary care. Table 2 also shows the number of unnecessary genetic tests, which are those that find a person does not actually have FH following a false positive clinical assessment. The highest

number of unnecessary genetic tests occur in Strategy 7 and relatively few occur in Strategy 3 and Strategy 4. In line with the specificity of each diagnostic criteria, there were more unnecessary genetic tests using the combined possible and definite SB criteria compared with the DLCN criteria using a score >5. The number of other, appropriate genetic tests is made up of true positive clinical assessments and relatives tested through cascade testing. Strategies that involve primary care database searching (3, 4, 7, 8) achieve similarly high numbers of appropriate genetic testing. These short term results highlight the trade-off between the diagnostic accuracy of the clinical assessment tools, the cost of, and setting in which, the strategies are implemented, and the need to consider long term results to determine the most cost-effective strategy.

**Figure 1: Base case short term outcomes, proportion of treated vs. untreated**

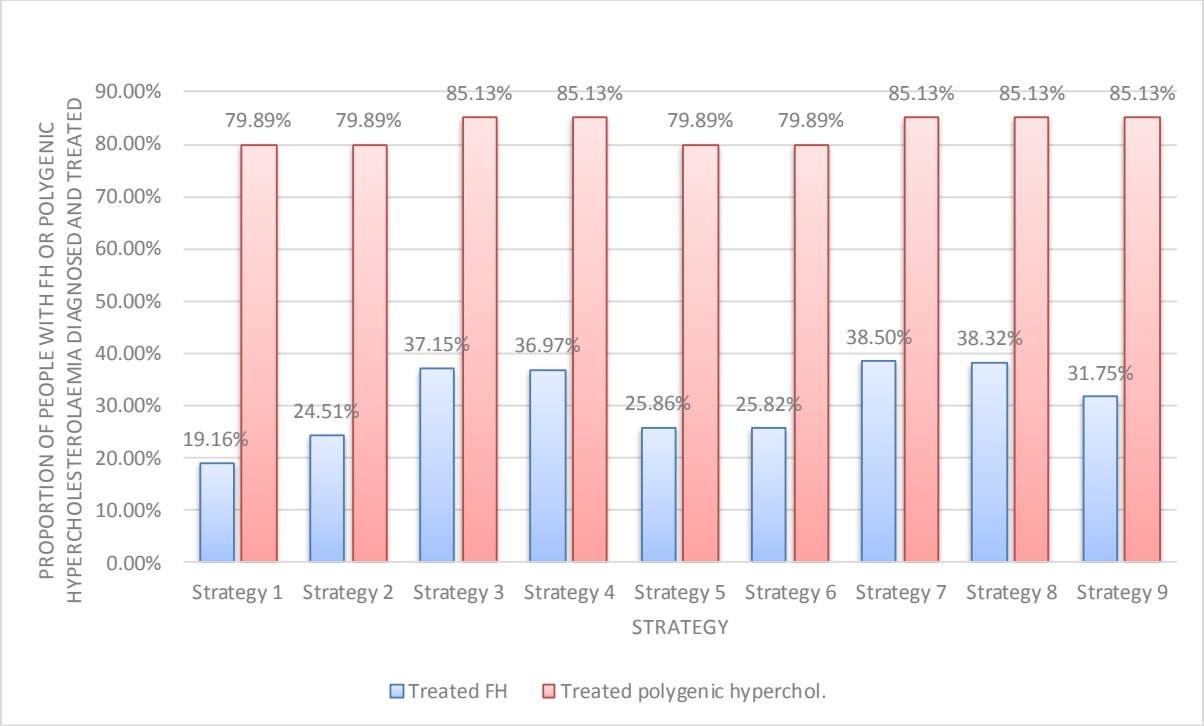


**Table 2: Total short term economic cost, base case**

| Strategy | Primary care | Secondary care | Genetic testing | Total short term cost | Number of unnecessary genetic tests | Cost of unnecessary genetic tests | Number of other genetic tests | Cost of other genetic tests | False negatives missed by clinical assessment |
|---|---|---|---|---|---|---|---|---|---|
| **1. No cascade testing and no case identification** | - | - | - | £0 | 0 | £0 | 0 | £0 | 0 |
| **2. Cascade testing** | £0 | £4,919,686 | £6,220,205 | £11,139,892 | 0 | £0 | 19,763 | £6,220,205 | 0 |
| **3. Primary care case identification, clinical assessment with SB criteria** | £2,446,705 | £8,975,760 | £10,793,647 | £22,216,112 | 7,226 | £2,709,936 | 27,935 | £8,083,711 | 1,666 |
| **4. Primary care case identification, clinical assessment with DLCN criteria** | £2,607,297 | £8,586,321 | £10,086,798 | £21,280,417 | 5,503 | £2,063,808 | 27,669 | £8,022,990 | 2,105 |
| **5. Secondary care case identification, clinical assessment with SB criteria** | £0 | £20,498,803 | £26,744,760 | £47,243,563 | 53,486 | £20,057,415 | 21,812 | £6,687,345 | 150 |
| **6. Secondary care case identification, clinical assessment with DLCN criteria** | £0 | £20,429,396 | £21,947,266 | £42,376,662 | 40,734 | £15,275,142 | 21,745 | £6,672,124 | 189 |
| **7. Primary and secondary care case identification, clinical assessment with SB criteria** | £2,446,705 | £24,554,877 | £31,318,202 | £58,319,784 | 60,713 | £22,767,351 | 29,984 | £8,550,851 | 1,816 |
| **8. Primary and secondary care case identification, clinical assessment with DLCN criteria** | £2,607,297 | £24,096,031 | £25,813,859 | £52,517,187 | 46,237 | £17,338,951 | 29,651 | £8,474,909 | 2,294 |
| **9. Primary care case identification, no cascade testing from new index cases** | £2,351,161 | £4,919,686 | £6,220,205 | £13,491,052 | 0 | £0 | 19,763 | £6,220,205 | 0 |

## Long term results

After adjusting for age, the Markov modules resulted in the mean payoffs for the four cohorts (see Supplementary Material). These figures represented the expected total, discounted cost and health outcomes experienced by each cohort over their lifetimes. Differences in QALYs and costs between males and females were predominantly due to different baseline risks of cardiovascular events and different adjustments in those risks due to FH. The figures show that if a case of FH can be found, it is highly cost effective to treat. Indeed, it may be cost saving especially for women of all ages and younger men due to the large reduction in CVD event costs outweighing the cost of high intensity statins.

## Short and long term results combined

Strategy 3 was the most cost-effective strategy with an incremental cost-effectiveness ratio (ICER) of £13,365 per QALY. Strategy 4 had an ICER of £3,254 per QALY but Strategy 3 was preferred because it maximised health gain up to NICE's £20,000 per QALY threshold. However, the total costs and QALYs for Strategies 3 and 4 are very similar. Strategy 2 (cascade testing only) had an ICER of £4,740 per QALY compared with Strategy 1 (no intervention) but was extendedly dominated by Strategy 4 compared with Strategy 1. Strategies 5 and 6 were excluded through simple domination as Strategies 3 and 4 provided more health benefits at less cost. Strategies 7 and 8 had ICERs of £63,514 per QALY and £82,388 per QALY respectively, well above NICE's cost effectiveness threshold. The cost-effectiveness frontier shows that although Strategies 9 and 4 are cost effective relative to Strategy 1, Strategy 3 is the most cost effective before the ICERs exceed the cost-effectiveness threshold for Strategies 7 and 8.

**Table 3: Incremental results, base case**

| Strategy | Cost (£) | QALYs | ICER |
|---|---|---|---|
| **1. No cascade testing and no case identification** | 6797.32 | 11.4079 | £0 |
| **2. Cascade testing** | 6843.092 | 11.41755 | Ext.Dom |
| **9. Primary care case identification, no cascade testing from new index cases** | 6851.824 | 11.45383 | £1,186 |
| **4. Primary care case identification, clinical assessment with DLCN criteria** | 6882.477 | 11.46325 | £3,254 |
| **3. Primary care case identification, clinical assessment with SB criteria*** | 6886.718 | 11.46357 | £13,365 |
| **6. Secondary care case identification, clinical assessment with DLCN criteria** | 6982.246 | 11.41991 | Dominated |
| **5. Secondary care case identification, clinical assessment with SB criteria** | 7004.111 | 11.41999 | Dominated |
| **8. Primary and secondary care case identification, clinical assessment with DLCN criteria** | 7021.597 | 11.4657 | £63,514 |
| **7. Primary and secondary care case identification, clinical assessment with SB criteria** | 7047.737 | 11.46601 | £82,388 |

QALY: Quality-adjusted life year; ICER: Incremental cost-effectiveness ratio (calculated by dividing the difference in costs by the difference in QALYs for each strategy compared with the next best alternative strategy, excluding dominated and extendedly dominated options);

* Indicates the most cost-effective strategy because it maximises health gain up to the cost-effectiveness threshold, £20,000/QALY

Strategies are listed in order of increasing mean cost to assist with the reporting and interpretation of incremental analysis.

## Sensitivity analysis results

The results of one-way sensitivity analyses conducted for 12 parameters were ranked by NMB (see Supplementary Material). When the prevalence of FH in people identified for further investigation in primary care was decreased to 15%, Strategy 4 became the most cost-effective strategy with Strategy 3 ranked second. When the prevalence of FH in people with early MI was increased to an upper estimate of 8.3%, Strategy 8, primary care and secondary care case identification with clinical assessment using the DLCN criteria, became the most cost-effective strategy. The threshold at which Strategy 3 no longer had the maximum NMB was around 4.3% (compared with a base case of 1.3%). When the proportion of people in primary care databases for who data is available was increased to 100% from the base case of 31%, Strategy 3 remained the most cost-effective option, although this had the expected consequence of very directly affecting the short term resource impact. The proportion of people already taking lipid modification pre-intervention was varied from 10% to 99% and made no difference to the order of preferred strategies. When the SB and DLCN criteria were varied to 'definite only' criteria it resulted in less net monetary benefits compared with the more inclusive criteria. When the number of relatives approached for cascade testing per index case was increased to the maximum of 12, Strategies 7 and 8 became the most cost effective. Threshold analysis revealed that the preferred strategies change once 8 relatives are contacted per index case, which is 4 times the base case value. An alternative search criteria requiring people to have total cholesterol > 9.3 mmol/L and triglycerides < 2.3 mmol/L before clinical assessment did not change the ranking of strategies but did slightly decrease the total resource impact of case identification strategies due to a lower number of people requiring clinical assessment. When the CHD relative risk due to FH was arbitrarily doubled and halved, the relative cost effectiveness between strategies did not change. When the risk of CHD events was matched to those observed in the SAFEHEART study (7.53% vs. 15-44% in the base case), the cost-effectiveness conclusions of the model remained largely the same.

## Probabilistic sensitivity analysis

Probabilistic sensitivity analysis indicated that Strategy 3 had a 57% probability of being the most cost-effective option at a threshold of £20,000 per QALY (Table 4). Strategy 4 had a 41% probability of being the most cost effective option, although the confidence intervals of NMBs for these two strategies overlapped almost exactly.

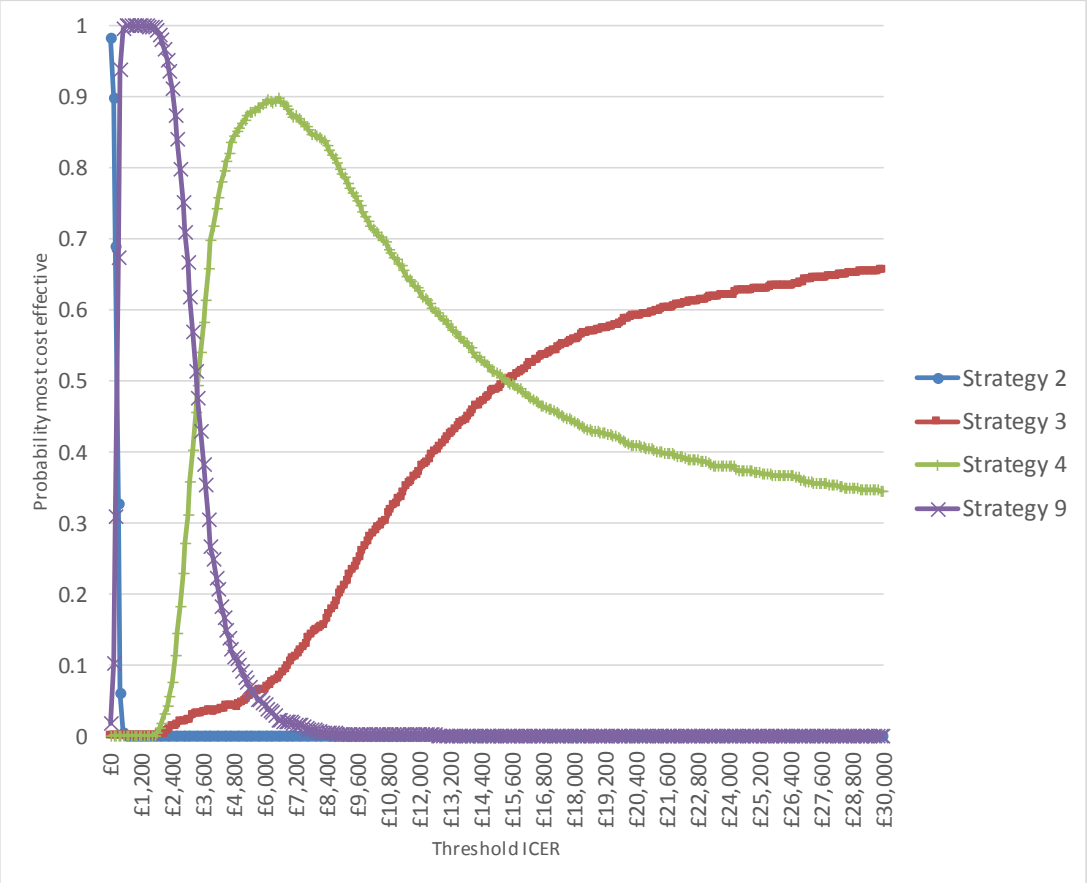
The cost-effectiveness acceptability curve shows the probability of selected strategies (2, 3, 4 and 9) being cost effective at different thresholds relative to other selected thresholds (Figure 2). Three strategies were selected for this analysis based on their deterministic results. Strategy 4 had the highest probability of being cost effective up to a threshold ICER of £17,000 per QALY. Strategy 3 had the highest probability of being cost effective up between ICERs of £17,000 and £30,000 per QALY.

**Table 4: Results of probabilistic sensitivity analysis**

| Strategy | NMB | | | Probability most cost effective |
|---|---|---|---|---|
| | Mean | Lower 95% CI | Upper 95% CI | |
| 1. No cascade testing and no case identification | 222,016 | 207,292 | 234,828 | 0.00% |
| 2. Cascade testing | 222,165 | 207,406 | 235,010 | 0.00% |
| 3. Primary care case identification, clinical assessment with SB criteria | 223,029 | 208,557 | 235,617 | 56.80% |

| | | | | |
|---|---|---|---|---|
| 4. Primary care case identification, clinical assessment with DLCN criteria | 223,027 | 208,539 | 235,617 | 40.70% |
| 5. Secondary care case identification, clinical assessment with SB criteria | 222,051 | 207,280 | 234,879 | 0.00% |
| 6. Secondary care case identification, clinical assessment with DLCN criteria | 222,072 | 207,302 | 234,913 | 0.00% |
| 7. Primary and secondary care case identification, clinical assessment with SB criteria | 222,915 | 208,478 | 235,464 | 0.10% |
| 8. Primary and secondary care case identification, clinical assessment with DLCN criteria | 222,936 | 208,483 | 235,493 | 2.40% |
| 9. Primary care case identification, no cascade testing from new index cases | 222,875 | 208,247 | 235,562 | 0.10% |

**Figure 2: Cost-effectiveness acceptability curve**




## Discussion

This economic analysis found that searching primary care databases and providing clinical assessment using the SB diagnostic criteria in addition to cascade testing was cost effective with an ICER of £13,365 per QALY (compared with Strategy 4) and a 57% probability of being cost effective. Clinical assessment using the DLCN criteria following primary care database searching had a 41% probability of being the most cost-effective strategy with costs and QALYs that were very close to the SB option (Strategy 3). The addition of primary care case finding to cascade testing therefore had a 95% probability of being cost-effective and absolute differences in costs and QALYs between the

DLCN and SB criteria were small. Analysis of the total short term resource impact showed that primary care case identification can be implemented at a cost of £22 million and diagnose over 7,700 people with FH. By contrast, the addition of case identification in secondary care would cost double this amount and is unlikely to be cost effective based on a prevalence of FH in people with a history of MI of 1.3%.

The analysis confirmed the cost effectiveness of cascade testing compared with no cascade testing with an ICER of £4,470 per QALY and 100% likelihood the strategy is cost effective at a threshold of £20,000 per QALY, confirming the conclusions of previous economic analyses.[6-9] However, additional health benefits are achievable at an acceptable cost by adopting case identification strategies in primary care in addition to cascade testing. The results were robust to one-way sensitivity analysis of the cost of genetic testing, realistic numbers of relatives approached for cascade testing and take up rates across all subgroups. Where cost-effectiveness results changed, primary care case identification remained cost effective and only the preferred diagnostic criteria changed. Referring both possible and definite cases of FH for genetic testing based on the SB criteria from primary care remained cost effective compared with referring only definite cases because the long term consequences of missed FH diagnoses outweighed the short term cost savings made available by referring definite cases only.

The dominant role of primary care identification compared with secondary care identification was altered if the prevalence of people with premature MI increased. If the prevalence of FH in people with MI was over 4%, expanding case identification to secondary care settings in addition to primary care settings and cascade testing may be cost effective. This parameter (1.3%) was informed by the only study identified in the literature at the time of analysis that investigated the prevalence of genetically-confirmed FH in this population, with a cohort of 231 patients.[24] However, a recent study of 103 patients suggests that the prevalence of genetically-confirmed FH in this population could be as high as 8.9%.[30] In the present analysis, the highest prevalence used in sensitivity analysis was 8.3% but this was based on clinical diagnosis, and thus overestimates the true prevalence of genetically-confirmed FH.[25] The present analysis clearly demonstrates the importance of research to identify the true prevalence of genetically-confirmed FH in people with a history of MI.

There are a number of advantages to this analysis. To our knowledge, it is the first time case identification in addition to cascade testing has been compared with cascade testing alone. In addition, a novel meta-analysis based on a systematic review of the diagnostic accuracy of clinical assessment tools compared with genetic testing was used to inform the model. The lifetime impacts of treating FH and polygenic hypercholesterolaemia were taken into account. The calculation of total short term resource impact is an additional important contribution to the evidence available to decision-makers. The treatment effect following diagnosis of FH was based on the reduction of the risk of CHD events only. This was a conservative approach as additional reduction in non-CHD mortality are likely due to lifestyle changes motivated by a person's knowledge of their FH status.[3] The NICE Guideline Committee viewed the number of relatives invited for cascade testing as quite conservative as it was based on an incomplete national cascade testing service. Families are geographically spread and, if most of the relatives for any given index case are in an area that does not have a FH service, then the yield from the index case is minimal. In the committee's view it is possible to achieve a higher yield from cascade testing if it is provided across England.

Interpretation of these results needs to take into consideration that cost effectiveness of the primary care case identification strategies in this model was influenced by the number of people

with polygenic hypercholesterolaemia that come into contact with primary care as a result of the interventions. Although the guideline update focused on familial hypercholesterolaemia, the NICE Guideline Committee took the view that the polygenic index cases would be impacted by the interventions and should continue to be included in the model.

This analysis has a number of limitations, mainly related to the assumptions required to operationalise the model. Genetic testing was assumed to have perfect sensitivity and specificity. This was a limitation common to all strategies so was thought not to affect overall conclusions, however, it marginally favoured the SB criteria due to undervaluing the costs of its lower specificity. A single probability of take up was used to represent take up across the entire care pathway. Factoring in differential take up rates may either increase or decrease the relative cost effectiveness of interventions depending on setting and where they occur in the care pathway. Adherence to lipid modification treatment was assumed to be 100%. This may have overestimated the cost effectiveness of all interventions compared with no intervention, although given that ranking of the strategies was completely insensitive to the number of people already taking statins within the model, this limitation was assessed as minor. The minimum starting age was 40 as this was the lowest age adopted in NICE's lipid modification model and aligns with the NHS vascular check programme. This limitation likely led to an underestimation of the cost effectiveness of all strategies due to the increased risk of CHD at younger ages due to FH. There was uncertainty as to the true relative risk of CHD and relative treatment effect between people with and without FH among those with a total cholesterol of >9.3 mmol/L, however, various theoretical data were tested in sensitivity analysis but this did not affect conclusions. There were also no data to inform the distribution of risk scores in the target population but the rankings were insensitive to extreme high and low values so this limitation was considered minor. Further, overlap of strategies was not accounted for. It is likely that an intervention of primary care case identification will identify people that have already been diagnosed with FH through cascade testing, and vice versa. However, no data were identified in the literature to inform the inclusion of this into the model. Finally, the take up of clinical assessment by people identified by a primary care database search was informed by an Australian study and may not be generalizable to other populations.[14]

It is possible that more accurate database search criteria exist in the literature.[31] However, they could not be used to inform this model due to diagnosis of FH being based on clinical assessment rather than genetic testing, leaving the true prevalence of FH within these populations uncertain. Further research in this area has the potential to ensure primary care resources are focussed on those people most likely to have FH by establishing the accuracy of database search algorithms based on genetically-confirmed diagnoses. Further research into the most effective case-finding methods would be of high value. This research could also be used to clarify which clinical assessment tool is the most appropriate for use in primary care.

Another area that should be prioritised for further research is the prevalence of FH in people with a history of MI. This analysis has shown the cost effectiveness of secondary care case identification strategies is contingent on this figure. The short term resource impact of secondary care case identification was estimated to be at least £30 million and has the potential to diagnose thousands of people with FH, but cannot be currently regarded as cost effective due to the inconsistent nature of the evidence.

## Conclusion

The identification of FH by analysing primary care databases in addition to cascade testing is likely to be a cost effective strategy. The SB criteria is likely to be more cost effective than the DLCN criteria although the results for both are similar. Strategies that involve case identification in people with early MI are unlikely to be cost effective given the current state of evidence on the prevalence of FH in people with a history of MI. This cost-effectiveness analysis provides sufficient evidence to suggest GPs develop a formalised method to assess for FH using one of the diagnostic criteria with a low threshold for referral, specifically both possible or definite when using the SB criteria, or scores >5 when using the DLCN criteria.

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