Universal screening at age 1-2 years as an adjunct to cascade testing for familial hypercholesterolaemia in the UK: a cost-utility analysis

Short title: Cost-effectiveness of universal screening for familial hypercholesterolaemia

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Abstract

Background The natural history of familial hypercholesterolaemia (FH), benefit of early intervention, and under-diagnosis, present a case for screening. Cascade testing (CT) of relatives has been shown to be feasible, acceptable and cost-effective in the UK, but is dependent on a supply of index cases. Feasibility of universal screening (US) at age 1-2 years was recently demonstrated. We examined whether this would be a cost-effective adjunct to CT in the UK, given the current and plausible future undiagnosed FH prevalence.

Methods Seven cholesterol and/or mutation-based US ± reverse cascade testing (RCT) alternatives were compared with no US in an incremental analysis with a UK NHS perspective. A decision model was used to estimate costs and outcomes for cohorts exposed to the US component of each strategy. RCT case ascertainment was modelled using recent UK CT data, and probabilistic Markov models estimated lifetime costs and health outcomes for the cohorts screened under each alternative. 1,000 Monte Carlo simulations were run for each model, and average outcomes reported. Further uncertainty was explored deterministically. Threshold analysis investigated the association between undiagnosed FH prevalence and cost-effectiveness.

Findings A strategy involving cholesterol screening followed by diagnostic genetic testing and then RCT was the most cost-effective alternative modelled (incremental cost-effectiveness ratio (ICER) versus no screening £12,480/quality adjusted life year (QALY); probability of cost-effectiveness 96·8% at £20,000/QALY threshold). Cost-effectiveness was robust to the deterministic sensitivity analyses, and threshold analysis suggested that sequential cholesterol screening-genetic testing plus RCT would remain cost-effective even if ongoing case ascertainment reached theoretical maximum levels.

Interpretation These findings support implementation of universal cholesterol screening followed by diagnostic genetic testing and RCT for FH, under a UK conventional willingness-to-pay threshold.

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Research in context

Evidence before this study

In the UK, fewer than 15% of those with familial hypercholesterolaemia (FH) have been diagnosed. Cascade testing of relatives has been recommended in the UK for several years, and has been shown to be feasible, acceptable and cost-effective, but requires a supply of index cases. Index cases could potentially be supplied by universal screening, which has recently been shown to be feasible at age 1-2 years.

Added value of this study

This study suggests that universal screening of the UK population at 1-2 years would be cost-effective. Of several screening alternatives modelled, cholesterol screening followed by diagnostic genetic testing plus reverse cascade testing was found to be the most cost-effective. Although a successful screening programme would reduce its own cost-effectiveness by reducing undiagnosed disease prevalence and therefore pre-test probability of disease, our findings indicate that universal screening would remain cost-effective even if it continually achieved maximum plausible case ascertainment.

Implications of all the available evidence

Taken together with demonstrated feasibility and indications of acceptability of universal screening, these findings support implementation of universal screening for FH at 1-2 years, in the UK.

Introduction

Familial hypercholesterolaemia (FH) is characterised by elevated low-density lipoprotein cholesterol (LDL-C) from birth, and is associated with elevated risk of coronary heart disease (CHD).[1] A recent general population study described an odds of CHD for the average untreated FH phenotype around 13-fold higher than that of the non-FH phenotype.[2] This relative risk is age-dependent, being higher in younger age-groups.[3] Mortality at <30 years is typical of untreated homozygous disease,[4] whereas the heterozygous genotype confers approximately 50% risk of CHD by 50 years among males, and 30% risk of CHD by 60 years in females.[5,6] Recent prevalence estimates for heterozygous disease range from 1/250-1/200 (1/300,000-1/160,000 for homozygous disease).[7,8] It is therefore anticipated that there are approximately 187,500-328,200 people with FH in the UK, but estimates suggest fewer than 15% have been diagnosed.[9,10] Those undiagnosed represent a substantial reservoir of potentially modifiable cardiovascular disease (CVD) risk.

The aim of FH treatment is LDL-C reduction via lifestyle modification and lipid modifying therapy (LMT). Limited trial data has constrained treatment at young ages, but recent studies support early intervention. Legacy effects from statin trials indicate greater treatment benefit with earlier initiation.[11] Young people with treated FH exhibit longer event-free survival than their affected parents, who experienced relative delay to statin therapy;[12] and recent trials have demonstrated statin impact on carotid intima-media thickness (a measure of carotid atherosclerosis) in childhood, with younger age of therapy initiation associated with more limited atherosclerotic progression.[13] Although only short term efficacy and safety data are available,[14,15] the data supporting early treatment, the premature, often unheralded consequences of FH, and widespread under-diagnosis,[9] have led to recommendations for screening and early treatment.[9,16]

Since 2008, the UK National Institute for Health and Care Excellence (NICE) has recommended cascade testing (CT, of first-, second- and third- degree relatives) for FH,[16] and this has been shown to be feasible, acceptable and cost-effective.[17,18] There has been limited roll-out of CT in England, as local teams have not commissioned the relevant services, but it has been relatively successful in other parts of the UK.[19] As CT depends on index case supply, there is interest in screening to identify index cases. Both adult and childhood systematic population screening (or 'universal screening'; US) for FH remain under review by the UK National Screening Committee (NSC). Recent NSC external review has considered that the NHS Health Check may

represent an adulthood FH screening mechanism,[20] but we are unaware of data supporting this. Moreover, the reach of Health Checks is restricted and increasingly so under the current contraction of UK local public health budgets.[21,22] Feasibility of otherwise screening in adulthood has not been demonstrated, and no model for adult screening has been described. There are also theoretical reasons to favour screening in childhood. The false positive and false negative FH case detection rates for given cholesterol thresholds appear to be most favourable at young ages,[23] and screening at younger ages enables intervention at an early stage of atherosclerosis development, when maximum benefit can still be obtained via lifestyle adaptations and LMT. The feasibility of US at age 1-2 years has recently been demonstrated,[24] but cost-effectiveness is unclear.

We therefore aimed to determine whether US for FH at 1-2 years could be a cost-effective adjunct to CT in the UK. Our main objective was to compare the cost-effectiveness of cholesterol and/or mutation-based US ± reverse cascade testing (RCT; where feasible) alternatives (detailed in Box 1), at current undiagnosed FH prevalence. We also examined whether there would be a point at which US would lose cost-effectiveness (due to falling FH prevalence as a result of screening and CT).

Box 1: Universal screening alternatives considered

1. No universal screening (allows for any ongoing cluster testing)
2. Cholesterol screening
3. Sequential genetic testing-cholesterol screening (i.e. genetic testing followed by cholesterol screening among mutation-positive individuals)
4. Sequential cholesterol screening-genetic testing (i.e. cholesterol screening followed by genetic testing among cholesterol-positive individuals)
5. Parallel cholesterol screening–genetic testing (i.e. cholesterol screening coincident with genetic testing)
6-8. Comparators 3-5, respectively, plus reverse cascade testing

NB. It was assumed all strategies would include assessment against clinical diagnostic criteria, hence only comparator two would result in some individuals being partially tested against standard UK diagnostic criteria and at risk of false positive results

Methods

Comparators, approach and perspective

The alternatives described in Box 1 were compared (with reference to heterozygous FH only) from a UK NHS healthcare perspective. Methods were aligned with the NICE reference case so far as possible,[25] in an incremental analysis that estimated lifetime (to a maximum of 100 years) costs and health outcomes (discounted at 3·5% per annum) for cohorts screened under each alternative. Where possible, modelling was based on UK data, and UK diagnostic criteria and treatment pathways. In the base case, definition of FH (for treatment purposes) was therefore a Simon Broome diagnosis *plus* hypercholesterolaemia (defined as total cholesterol exceeding the general population 95th percentile).[26,27] All (and only) mutation-positive individuals were considered as index individuals for RCT

The model had three main components:

1. A decision tree estimated outcomes for cohorts of 10,000 1-2 year olds exposed to the US component of each alternative
2. Local CT data were used to estimate RCT case ascertainment, given the number of mutation-positive individuals identified in US, and
3. Markov models estimated lifetime costs and health outcomes for the cohorts screened under each alternative, in view of the number of diagnoses made

Data for parameter estimation were obtained from a systematic review (published 2000),[26] updated with a systematic literature search (detailed in Supplementary File 1) and data from a recent economic evaluation and the Welsh FH CT programme.[17,28] As relevant data were sparse, no formal syntheses were undertaken and model parameters were estimated conservatively.

Model structure and inputs

The decision tree used to model US (Figure 1a) reflects simplified versions of the screening pathway used in the recent UK study that demonstrated US feasibility.[24] The associated probabilities (Table 1) were combined to derive outcomes for each screening cohort (Supplementary File 2). We assumed there was no delay between US case-identification and RCT, and based on local data and an expectation that a US programme would facilitate improved CT,[24,29] estimated base case RCT yield was two mutation-positive individuals per mutation-positive index individual. That is, where RCT was part of the screening alternative it was assumed two mutation-positive individuals would be identified via RCT for every mutation-positive individual identified in US. It

was assumed the age-distribution of those identified by RCT would be as observed in the Welsh CT programme,[17,28] and that 70% of RCT-identified mutation-positive relatives would meet the base case FH definition.[30-32] For purposes of costing RCT (see below), probability of mutation detection among relatives was assumed to be Mendelian.

Separate Markov models estimated outcomes for cohorts of 1,000 diagnosed or undiagnosed individuals, starting from age two years, five years, and each subsequent five-year interval to 85 years. The modelling approach followed that used in the economic evaluation for NICE CG181, and a recent CT analysis, and is described fully in Supplementary File 3.[17,33] Briefly, baseline CVD risks drew on the QRISK2 model,[34] and the modelled health states included all constituent diagnoses of the QRISK outcome (see Figure 1b). Where QRISK2 was not validated for age-groups of interest, CVD risks were estimated using age-related CVD relative risks calculated from published data.[35] The relative CHD death risks described for the pre-treatment era Simon Broome cohort were applied to the angina, MI and CHD death risks.[3] Individuals progressed to post-CVD states in the cycle following development of non-fatal CVD, unless a further event or death occurred immediately. Secondary event risks obtained from NICE CG181 (with some adjustments – see Supplementary File 3) were applied without adjustment for FH,[33] but the models did not allow for impact of multiple previous events. Non-CVD mortality was estimated from 2015 England and Wales Office for National Statistics mortality and mid-year population figures,[36,37] and it was assumed that CVD and mortality risks for the youngest age-group (not specifically reported), were zero. Modelled treatment was based on national guidance and local audit and registry data, and was modelled until age 60 years (details in Supplementary File 4).[10,16,38] Welsh FH audit age-band-specific pre-treatment LDL-C levels (concordant with national paediatric register data) were applied,[17] and 37% treatment-related LDL-C reduction modelled in the base case (as observed in the UK 2010 national FH audit,[10] cf. 35% in paediatric register).[38] Resultant expected treatment-related absolute LDL-C reductions were transformed to CVD relative risk reductions using the Cholesterol Treatment Trialists' (CTT) Collaboration-reported per mM values for non-fatal MI, ischaemic stroke, and CHD death (applied to angina and MI, TIA and stroke, and CHD death, risks, respectively).[39] The CTT values were assumed applicable to both primary and secondary events.

Cycle health state outcomes were weighted with the utilities described in CG181,[33] and costs and effects were discounted, enabling calculation of discounted quality-adjusted

life year (QALY) and cost outcomes for each model. Models assumed no FH- or LMT-associated disutility, as per previous observation,[40,41] and assumption that treatment-related disutility would prompt treatment modification, averting its persistence. To determine overall Markov model outcomes for each alternative, the outcomes from each model were combined according to the age-distribution and diagnosed/undiagnosed status of the individuals identified by US and RCT in at least one of the screening scenarios, for each alternative.

Resource use and costs

Costs were calculated in 2017 GBP. Modelled costs were current where possible, otherwise inflated to 2017 values, and assumed to remain constant (subject to discounting) over the model duration. Table 2 summarises the costs applied. Total US costs were estimated for each cohort by multiplying individual costs*probability of being incurred under the relevant strategy*10,000. CT costs per index individual were estimated as the costs of index individual consultation, plus screening costs for identified relatives (based on CG71 CT recommendations and associated costing template)*the inverse of the probability of a relative being affected. Patient monitoring costs were applied only when patients were receiving LMT, except in cases of LMT-naïve individuals <18 years. At all ages, annual monitoring included blood sampling, lipid profile testing, and medical review (secondary care review at <18 years; 80:20 secondary:primary care split at ≥18 years).[10,29] Creatine kinase and 2x liver function tests were costed for the first treatment year, plus an additional secondary care review if this was not the screening year.

Management of uncertainty and calculations

To include parameter uncertainty, Markov models were built probabilistically, with beta distributions applied for transition probabilities and utilities, log-normal distributions for the CVD relative risks associated with FH and LDL-C reduction, and normal distribution for the pre-treatment LDL-C estimates (details in Supplementary File 5). 1,000 Monte Carlo simulations were run for each model. Uncertainty was further explored in a series of one-way DSAs, as outlined in Table 3, and the impact of including treatment costs for false positives identified in the cholesterol-only screening alternative (assuming treatment as per true positives, with estimated survival based on current standard life tables),[42] was also considered.

In all analyses, ICERs were calculated for each alternative versus the next lowest cost. Dominated comparators were excluded and the remaining alternatives compared to

the remaining next lowest cost, repeated as necessary. Cost-effectiveness was assessed using the £20,000-£30,000 NICE willingness-to-pay threshold,[25] and cost-effectiveness acceptability curves were plotted. Threshold analysis estimated the undiagnosed FH prevalences at which the ICER for the most cost-effective screening strategy crossed £20,000/QALY and £30,000/QALY willingness-to-pay thresholds, under otherwise base case conditions ± off-patent LMT costs (see Table 3). Scenarios in which CT yields were 2·4, 6·1 and 8·6 cases/index, and undiagnosed FH prevalences were 67, 33 and 24%, respectively, were also considered, as theoretical analyses indicate that such undiagnosed prevalences could not be reached with these CT yields.[43] Analyses were carried out using MS Excel v14.7.7.

Results

The sequential cholesterol screening-genetic testing plus RCT strategy was the most cost-effective in all analyses, and no scenario identified an additional strategy that could be cost-effectively provided. The number of FH cases identified under each screening strategy, costs per diagnosis, average QALYs gained, overall costs, and associated ICERs, are displayed in Table 4 (DSA estimates in Supplementary Files 6 and 7). Diagnosis rates ranged from 11·4/10,000 screened (sequential genetic testing-cholesterol screening) to 25·4/10,000 (parallel cholesterol screening-genetic testing) without RCT, and 31·1/10,000 to 45·1/10,000 (same US strategies) with RCT. Costs per US diagnosis ranged from £11,788 (cholesterol-only screening) to £217,036 (sequential genetic-cholesterol screening). Cost per RCT diagnosis was £1,110. The lowest overall cost per diagnosis (£8,886) was observed for the sequential cholesterol screening-genetic testing plus RCT strategy, which also achieved the second highest number of diagnoses (39·8/10,000). The ICER for this strategy versus no screening (£12,480/QALY) dominated all others except the parallel cholesterol-genetic US plus RCT scenario (ICER for direct comparison =£399,581/QALY).

As expected, ICERs were sensitive to RCT success, ranging from £6,269-£6,729/QALY to £18,253/QALY across the RCT yields tested. Discounting at 1·5%, and 50% treatment-related LDL-C reduction, were associated with relatively low ICERs (£5,489/QALY and £7,733/QALY, respectively). Only discounting at 5% produced an ICER >£20,000/QALY (£20,849/QALY). Cost-effectiveness acceptability curves for the sequential cholesterol screening-genetic testing US plus RCT versus no screening comparison are displayed for several scenarios in Supplementary File 8. For the base case, probability of cost-effectiveness was 96·8% at a willingness-to-pay threshold of £20,000/QALY (100% at £30,000/QALY).

Threshold analysis suggested US would be cost-effective at a £20,000/QALY threshold until undiagnosed prevalence reached <48% (<30% for £30,000/QALY threshold). Corresponding prevalences were <43% and <28% with off-patent LMT costs. ICERs for the scenarios in which undiagnosed prevalences of 67%, 33% and 24%, and respective CT yields of 2·4, 6·1 and 8·6 cases per index, were modelled, were £13,692/QALY, £14,630/QALY and £15,680-£16,146/QALY, respectively (£11,745/QALY, £12,851/QALY and £13,653-14,115/QALY with off-patent LMT costs).

Discussion

Summary of findings

This study aimed to assess which of seven potential FH US strategies would be most cost-effective for the UK context, whether any would be cost-effective as per conventional NICE definition, and whether US could reduce undiagnosed FH prevalence to levels at which it would lose cost-effectiveness. Sequential cholesterol screening-genetic testing plus RCT was the most cost-effective alternative modelled, and cost-effectiveness was robust to DSAs and to reductions in undiagnosed prevalence that US could theoretically achieve.[43] The modelled approach - with screening incorporated into routine child healthcare appointments – is efficient in terms of minimising user inconvenience, limiting additional healthcare costs, and potentially promoting screening engagement. As cholesterol results can be obtained by a point-of-care testing method, individuals with cholesterol levels below the threshold that would trigger genetic testing could be immediately reassured. While a mutation is only detected in a proportion of those with LDL-C above the threshold, a mutation confirms the diagnosis for these individuals, and unequivocal DNA-based diagnostic testing of relatives (so-called reverse cascade testing) can be undertaken. The clinical value of the approach is achieved by provision of LMT at a relatively young age, before high LDL-C burden has resulted in premature atherosclerosis and a CHD event.

Comparison with existing literature

Among 10,000 children eligible for US, the sequential cholesterol screening-genetic testing plus RCT strategy we found to be most cost-effective identified fewer children with hypercholesterolaemia plus an FH mutation (n=10.98) than reported per 10,095 children from the recent US feasibility study (n=21 such cases identified).[24] This may be explained by the fact that we accounted for non-attendance and non-participation, required hypercholesterolaemia on two rather than one tests (i.e. accounted for biological and analytical cholesterol variability), and used a slightly more restrictive definition of hypercholesterolaemia. Chance may also be relevant as the numbers are small. Reported costs per diagnosis were lower ($2,900 and £3,500) in recent studies than in our study, but this discrepancy is expected as in addition to the test costs ± limited consultation time they considered, we allowed for more screening consultation time (as recommended by local clinicians familiar with FH testing), administrative costs, and initial specialist review.[24,44] We did not find further recent estimates of diagnosis costs or US cost-effectiveness in children, but a 2002 HTA estimated both for US at 16 years.[26] Comparability is limited by inflation and methodological differences. Nonetheless, reported costs per diagnosis from the 2002 study were

£9,754 where clinically confirmed and £72,140 with genetic confirmation,[26] and the corresponding costs per life year gained, (with discounting at 3%), £7,244 and £33,882.[45] Given the interim reductions in genetic screening costs, these values probably support that those reported here are feasible.

The ICER of £12,480/QALY for sequential cholesterol screening-genetic testing plus RCT is as expected higher than that recently estimated for CT from known cases (ICER = £5,806/QALY).[17,18] Although several parameters were modelled similarly in both analyses, the CT analysis did not model identification of index cases,[17,18] which depends on testing with a much lower pre-test probability of disease, and is therefore associated with higher screening costs per diagnosis. As US enables FH diagnosis at a relatively young age, the differential latencies to treatment and impact on the natural history of the disease will also contribute to the CT versus US cost-effectiveness differences.

Strengths and limitations

This study appears to be the first to consider the cost-effectiveness of universal screening for FH at 1-2 years. The study compared the multiple screening options previously noted of interest,[46] and recent local data were available to estimate several parameters.

The persistent uncertainty around the sensitivity and specificity of different cholesterol theresholds,[47] although considered in DSA, is an important limitation of all work in this area. Additional limitations in parameter estimation included the required extrapolation of treatment efficacy data from non-FH populations beyond the duration of LMT trials, and beyond the intermediate outcomes of paediatric trials, and extrapolation of the CTT relative risk reduction estimates beyond primary events. Secondary CVD event risk estimates were limited by the time lapsed since their description and lack of adjustment for FH. FH-specific utility data are few, and those applied (from non-FH populations) were drawn from studies that utilised a range of choice-based preference elicitation methods and samples (including non-UK-based samples). The model structure necessarily followed a simplified version of treatment pathways and did not include additional potential inputs such as dietetics and management of statin-attributable diabetes, which appears in any case to be low in FH patients.[48,49] The models also assumed no pre-existing CVD, which will not always be the case.[50] Additional methodological limitations included the one-way modelling of uncertainties in DSA, when some could theoretically be realised in combination, and the

'memoryless' characteristic of Markov models which constrained modelling of accumulating CVD burden.

Implications for research and practice

2016 NSC review recommended against US for FH. Lack of demonstrated cost-effectiveness was a concern, but also practical feasibility, acceptability, and lack of evidence that US would reduce morbidity and mortality.[51] Feasibility of direct demonstration of impact on morbidity and mortality has been questioned, as the ethical and time demands of clinical endpoint trials are likely unachievable. However, the feasibility of US has now been demonstrated, in a study that also indicated acceptability among parents,[24] and other studies have similarly found that participants generally consider such screening beneficial.[40,52-54] Together with our findings, which would conventionally (i.e. under the standard NICE threshold) support implementation of US, these studies support reconsideration of US. Cholesterol thresholds of alternative sensitivity/specificity (which may impact on US acceptability) could be considered in future analyses, when test performance at these thresholds has been described.

Conclusions

A sequential cholesterol screening-genetic testing plus RCT approach would be the most cost-effective FH US strategy for the UK. Although a successful screening programme would reduce undiagnosed FH prevalence and therefore screening cost-effectiveness, sequential cholesterol screening-genetic testing plus RCT would remain cost-effective even if it continually achieved maximum plausible case ascertainment.

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Ethics statement

As this study was a secondary analysis of published data, formal ethical approval was not required.

Contributorship

AJM and AM designed the study. AJM carried out the analyses and wrote the first draft of the manuscript. All authors provided input and approved the final version for submission.

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Declaration of interests

AJM, HH, DM and AM report no competing interests. SEH is the Medical Director and minority shareholder of a UCL spin-out company called StoreGene, which uses a 20 SNP genetic test, in combination with the classical risk factor profile, for estimating an individual's future risk of CVD, and which offers genetic testing for FH through an accredited diagnostic laboratory. SEH is a consultant for Color Genomics which offers genetic tests for FH in the US, and reports grants from the British Heart Foundation and International Atherosclerosis Society-Pfizer, outside the submitted work. SEH was one of the topic experts for the 2017 NICE FH guideline update of the 2008 FH guideline CG71. KKR reports grants from Sanofi, Regeneron, Amgen, Pfizer and MSD, outside the submitted work. KKR reports personal fees from Sanofi, Amgen, Regeneron, Pfizer, Kowa, Algorithm, IONIS, Esperion, Medicines Company, Novo Nordisk, Takeda, Boehringer Ingelheim, Resverlogix, Abbvie, Cerenis, Cipla, Mylan, Janssen and Lilly, outside the submitted work.

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Supplementary File 1: Systematic literature search – summary and example database search strategy

Search terms were chosen with the aim of identifying information related to FH screening, diagnostics, treatment, and CVD and mortality outcomes, as well as previous economic evaluations of FH screening. Results were limited to those published since 1999, and to systematic reviews and meta-analyses, clinical trials, observational studies, other evaluations including economic evaluations, case series, registry data, guidelines, government publications and technical reports, published in English. Reference lists of included papers were also searched and further searches were carried out using the names of authors active in the field.

The Medline (via Pubmed), Embase (via Ovid), Cochrane Library, Health Management Information Consortium, NICE Evidence, Cost-Effectiveness Analysis Registry, Paediatric Economic Database Evaluation, and Centre for Reviews and Dissemination Database of Abstracts of Reviews of Effect, NHS Economic Evaluation Database, and Health Technology Assessment databases were searched on 08/08/2017.

Keywords and additional terms used to generate database search strategies:

	Keyword	Additional terms
Population	Familial hypercholesterolaemia	Fredrickson hyperlipoproteinaemia, type IIa; Hyperbetalipoproteinaemia; Hyperlipidaemia, group A; Low-density-lipoprotein-type hyperlipoproteinaemia
Intervention	Mass screening[mesh]	Case-finding
Outcomes	Diagnostic tests, routine[mesh]	Symptom assessment[mesh]; Physical examination[mesh]; Medical history taking[mesh]; Clinical laboratory techniques[mesh]; Diagnostic errors[mesh]; Clinical decision-making[mesh]
	Genetic techniques[mesh]	Genotype[mesh]; Phenotype[mesh]; Genetic heterogeneity[mesh]; Mutation[mesh]; Polymorphism, genetic[mesh]; Genetic Counseling[mesh]
	CVD, mortality	Myocardial ischaemia[mesh]; cerebrovascular disorders[mesh]; peripheral arterial disease[mesh]; vital statistics[mesh]; death[mesh]
	Anticholesteremic agents[mesh]	Treatment outcome[mesh]

Example search strategy:

Terms and filters used to search the Medline database via Pubmed

1. familial hypercholesterolaemia[Title/Abstract] OR familial hypercholesterolemia[Title/Abstract]

2. cost and cost analysis[MeSH Terms] OR mass screening[MeSH Terms] OR diagnostic tests, routine[MeSH Terms] OR clinical chemistry tests[MeSH Terms] OR genetic testing[MeSH Terms] OR genotype[MeSH Terms] OR phenotype[MeSH Terms] OR genetic heterogeneity[MeSH Terms] OR mutation[MeSH Terms] OR polymorphism, genetic[MeSH Terms] OR genetic counseling[MeSH Terms] OR myocardial ischemia[MeSH Terms] OR cerebrovascular disorders[MeSH Terms] OR peripheral arterial disease[MeSH Terms] OR life expectancy[MeSH Terms] OR life tables[MeSH Terms] OR mortality[MeSH Terms] OR death[MeSH Terms] OR anticholesteremic agents[MeSH Terms] OR treatment outcome[MeSH Terms]
3. 1 AND 2

Filters applied:

1. Dates: 1999 – present
2. Article types: Clinical study, clinical trial (all phases), comparative study, consensus development conference, dataset, evaluation studies, government publications, guidelines, meta-analysis, multicenter study, observational study, practice guideline, pragmatic clinical trial, randomised controlled trial, systematic review, technical report, twin study, validation study

Supplementary File 2: Formulae applied in decision tree calculations

Formulae presented only for outcomes not equal to zero

FH+: familial hypercholesterolaemia (FH)-positive, as per base case definition
FH-: FH-negative, as per base case definition
M+: FH mutation-positive
M-: FH mutation-negative
TC+: total cholesterol test results positive
TC-: total cholesterol test results negative
A1: first screening appointment attendance
P1: screening participation at first appointment
A2: second screening appointment attendance
P2: screening participation at second appointment

Branch 1: No screening

Mutation status	Mutation status determined	Formula
False negatives		
M+	No	p(FH+)*p(M+|FH+)
M-	No	p(FH+)*p(M-|FH+)
True negatives		
M+	No	p(FH-)*p(M+|FH-)
M-	No	p(FH-)*p(M-|FH-)

Branch 2: cholesterol-only screening

Mutation status	Mutation status determined	Formula
True positives		
M+	No	p(FH+)*p(M+|FH+)*p(A1)*p(P1)*p(TC+|FH+)*p(A2)*p(P2)
M-	No	p(FH+)*p(M-|FH+)*p(A1)*p(P1)*p(TC+|FH+)*p(A2)*p(P2)
False negatives		
M+	No	p(FH+)*p(M+|FH+) - p(true positive, M+ status undetermined)
M-	No	p(FH+)*p(M-|FH+) - p(true positive, M- status undetermined)
True negatives		
M+	No	p(FH-)*p(M+|FH-) - p(false positive, M+ status undetermined)
M-	No	p(FH-)*p(M-|FH-) - p(false positive, M- status undetermined)
False positives		
M+	No	p(FH-)*p(M+|FH-)*p(A1)*p(P1)*p(TC+|FH-)*p(A2)*p(P2)
M-	No	p(FH-)*p(M-|FH-)*p(A1)*p(P1)*p(TC+|FH-)*p(A2)*p(P2)

Branch 3: genetic-only screening

Mutation status	Mutation status determined	Formula
True positives		
M+	Yes	p(FH+)*p(A1)*p(P1)*p(M+|FH+)*p(TC+|FH+)*p(A2)*p(P2)
False negatives		
M+	Yes	p(FH+)*p(A1)*p(P1)*p(M+|FH+) - p(true positive, M+ status determined)

M+	No	p(FH+)*p(M+|FH+) - p (true positive, M+ status determined) - p(false negative, M+ status determined)
M-	Yes	p(FH+)*p(A1)*p(P1)*p(M-|FH+)
M-	No	p(FH+)*p(M-|FH+) - p(false negative, M- status determined)
True negatives		
M+	Yes	p(FH-)*p(M+|FH-) - p(true negative, M+ status undetermined)
M+	No	p(FH-)*p(M+|FH-)*(1-p(A1)) + p(FH-)*p(M+|FH-)*p(A1)*(1-p(P1)) + p(FH-)*p(A1)*p(P1)*p(M+|FH-)*p(TC+|FH-)*(1-p(A2)) + p(FH-)*p(A1)*p(P1)*p(M+|FH-)*p(TC+|FH-)*p(A2)*(1-p(P2))
M-	Yes	p(FH-)*p(A1)*p(P1)*p(M-|FH-)
M-	No	p(FH-)*p(M-|FH-) - p(true negative, M- status determined)

Branch 4: sequential cholesterol-genetic screening

Mutation status	Mutation status determined	Formula
True positives		
M+	Yes	p(FH+)*p(A1)*p(P1)*p(TC+|FH+)*p(A2)*p(P2)*p(M+|FH+)
M-	Yes	p(FH+)*p(A1)*p(P1)*p(TC+|FH+)*p(A2)*p(P2)*p(M-|FH+)
False negatives		
M+	No	p(FH+)*p(M+|FH+) - p(true positive, M+ status determined)
M-	No	p(FH+)*p(M-|FH+) - p(true positive, M- status determined)
True negatives		
M+	No	p(FH-)*p(M+|FH-)
M-	Yes	p(FH-)*p(A1)*p(P1)*p(TC+|FH-)*p(A2)*p(P2)*p(M-|TC+)
M-	No	p(FH-)*p(M-|FH-) - p(true negative, M- status determined)

Branch 5: parallel cholesterol-genetic screening

Mutation status	Mutation status determined	Formula
True positives		
M+	Yes	p(FH+)*p(A1)*p(P1)*p(M+|FH+)*p(TC+|FH+)*p(A2)*p(P2)
M-	Yes	p(FH+)*p(A1)*p(P1)*p(M-|FH+)*p(TC+|FH+)*p(A2)*p(P2)
False negatives		
M+	Yes	p(FH+)*p(A1)*p(P1)*(M+|FH+) - p(true positive, M+ status determined)
M+	No	p(FH+)*p(M+|FH+) - p(true positive, M+ status determined) - p(false negative, M+ status determined)
M-	Yes	p(FH+)*p(A1)*p(P1)*p(M-|FH+) - p(true positive, M- status determined)
M-	No	p(FH+)*p(M-|FH+) - p(true positive, M- status determined) - p(false negative, M- status determined)
True negatives		
M+	Yes	p(FH-)*p(A1)*p(P1)*p(M+|FH-)*p(TC-|FH-)
M+	No	p(FH-)*p(M+|FH-) - p(true negative, M+ status determined)
M-	Yes	p(FH-)*p(A1)*p(P1)*p(M-|FH-)
M-	No	p(FH-)*p(M-|FH-) - p(true negative, M- status determined)

Supplementary File 3: Markov model details

Following estimation of case ascertainment under each screening strategy, the differential case ascertainment was described, with the individuals diagnosed under at least one strategy designated diagnosed or not, under each. A series of Markov models were designed to determine the average lifetime costs and effects associated with each designation (structure in Figure 1b). The models had annual cycles, with health state transitions at the start of each cycle, and all individuals entered in a 'well' health state (i.e. were without pre-existing CVD). Models were run separately for cohorts of 1,000 diagnosed or undiagnosed FH patients, with model entry at 2 years, 5 years, and each subsequent 5-year interval to 85 years.

US-identified individuals entered the model at 2 years. The age distribution of RCT-identified cases was presumed to follow that recently reported by the Welsh screening programme (in 0-19, 20-24, 25-34, 35-44, 45-54, 55-59, and 60-84 years categories; no individuals older than 84 years were identified; Kerr et al., 2017). And for modelling these cases were distributed equally across each of the Markov model start ages within the relevant age-category and that immediately above the upper limit of the category (to limit age underestimation).

Transition probabilities

Baseline annual primary CVD risks were estimated for each age-band by annualising the average of the 10-year QRISK2 estimates for all age-sex combinations within the age-band (Hippisley-Cox et al., 2008). The 10-year risks ($P_{10\text{-}year}$) were converted to rates using the formula:

$$\text{rate } (r) = (-\ln(1-P_{10\text{-}year}))/10$$

and the calculated rates converted into annual risks (P_{annual}) using the formula:

$$P_{annual} = 1 - e^{-r}$$

As FH enhances CHD risk, but may not increase risk of cerebrovascular disease, the overall CVD risk estimates were disaggregated into constituent condition-specific risks using the multiplication factors described in CG181 (originally based on the Bromley CHD Register and Oxfordshire Community Stroke Project data). The resulting CVD death risk estimates were further split into CHD and non-CHD CVD estimates, according to the proportion of CVD deaths (deaths recorded under ICD10 codes G45, I20-25, I50, I60-64, and I73) attributed to CHD (recorded under codes I20-25) in the 2015 England and Wales Office for National Statistics (ONS) mortality database. For ages below those for which QRISK2 is valid (25-84 years), baseline CVD risks were estimated by adjusting the 25-29 years risks using the relative risks of 2013-14 HES-recorded inpatient CHD episodes (applied to angina, MI and CHD death), stroke episodes (for TIA and stroke), and non-CHD CVD episodes (for non-CHD CVD death), among those in the age-band of interest compared with the 25-29 years group. The relative risks were calculated using the episode counts for England reported by Bhatnagar *et al* (2016), and denominators from the 2013-14 ONS English population estimates. Risks for the 80-84 years group were similarly adjusted to achieve estimates for the 85+ years group. It was assumed the relative CHD death risks described for the pre-treatment era Simon Broome cohort applied equally to fatal and non-fatal CHD, hence these were applied to the angina, MI and CHD death risks (Simon Broome Register Group, 1991). For age-bands below those for which relative risks were reported (20-79 years), the 20-39 year relative risk was applied (likely conservative as relative risk appears to decrease with age; Simon Broome Register Group, 1991) It was assumed those above 79 years did not experience any FH-

associated CHD risk, as observed for the 60-79 years group (Simon Broome Register Group, 1991).

The secondary event risks described in CG181 were also applied without adjustment for FH. These estimates were originally based on data from the Nottingham Heart Attack Register, South London Stroke Register, Juul-Moller et al, 1992, and the CURE trial. Undescribed required age-specific risks (for those <40 years) and CHD versus non-CHD CVD mortality risks, were estimated as described for primary CVD. As transition probabilities were not available for stable angina-stroke, unstable angina-unstable angina and TIA-unstable angina transitions, primary event risks were substituted. Primary event risks were also applied where they exceeded secondary event risks. It was assumed that probability of post-event state transitions to stable angina and TIA (i.e. improbable CHD regression) was zero. Non-CVD mortality risk was estimated using the 2015 England and Wales ONS mid-year population and non-CVD (i,e, total minus CVD) mortality figures. As HES data specific to the youngest modelled age-band were not available, it was assumed that CVD and mortality risks for this group were zero.

Treatment effects on transition probabilities were modelled as described in the main paper and Supplementary File 4. In the deterministic sensitivity analyses that involved modelling treatment discontinuation (see Table 3), it was assumed that transition probabilities reverted to untreated values immediately on discontinuation, which is likely conservative in view of treatment legacy effects (Ford et al., 2016).

Supplementary File 4: Details of modeled treatment

As no FH-associated risk was applied at ≥60 years of age (in the Simon Broome cohort no FH effect was identified in this group; Simon Broome Register Group, 1991) FH treatment was modelled only to 60 years. Following the 2010 UK national FH management audit, LMT use was modelled for 85% of FH-diagnosed adults in the base case (Pedersen et al, 2010). Modelled LMT regimes were also based on this audit, but with 40mg/day atorvastatin substituted for 80mg/day simvastatin regimes, in view of recent MHRA guidance to limit use of this regime (MHRA, 2010). It was therefore assumed that, among treated adults, 80% would use atorvastatin, 10% simvastatin, and 10% rosuvastatin, and that 46.3% would additionally use ezetimibe, with dose distribution as detailed below. It was assumed that children <8 years did not use LMT. Estimated proportions using LMT at 8-9 and 10-17 years were 23.1% and 57.6%, as per recent report from the UK paediatric FH register, which also provided information about the nature of treatment (Ramaswami et al., 2017). It was assumed all treatment at <10 years was with low-dose pravastatin, with the remaining LMT regimes reported applicable to those 10-17 years – detailed below.

	Proportions of treated persons using therapy		
Daily therapy	**≥18 years**	**10-17 years**	**8-9 years**
Atorvastatin 10 mg	0.08	0.366	0
Atorvastatin 20 mg	0.112	0.113	0
Atorvastatin 40 mg	0.32	0.038	0
Atorvastatin 80 mg	0.288	0.013	0
Rosuvastatin 5 mg	0.014	0.029	0
Rosuvastatin 10 mg	0.025	0	0
Rosuvastatin 20 mg	0.031	0	0
Rosuvastatin 40 mg	0.03	0	0
Simvastatin 10 mg	0.008	0.162	0
Simvastatin 20 mg	0.017	0.054	0
Simvastatin 40 mg	0.075	0	0
Simvastatin 80 mg	0	0	0
Pravastatin 10 mg	0	0.169	1.0
Pravastatin 20 mg	0	0.056	0
Pravastatin 40 mg	0	0	0
Ezetimibe 10 mg	0.463	0	0

Supplementary File 5: Probability distributions assigned to sampled parameters and associated statistics

[a]Standard errors estimated as 10% of the point estimate, as per previous models (NICE CG181; Ward et al, 2005) [27 53]; [b]Normal distribution was assigned to pre-treatment LDL-C estimates, as studies indicate such distribution (Starr et al., 2008, Wald et al., 2007), and CI limits were sufficiently high to avoid risk of impossible negative values; SE: standard error; MI: myocardial infarction; TIA: transient ischaemic attack; FH: familial hypercholesterolaemia; CHD: coronary heart disease; LDL-C: low density lipoprotein cholesterol; LL: lower limit; UL: upper limit; CI: confidence interval; SB: Simon Broome

Parameter	**Distribution**	**Statistics**					**References**
		Point estimate (E)	**SE**	**Alpha**	**Beta**		
Transition probabilities	Beta	As per text	0.1*annual risk[a]	E*(E*(1-E)/ (SE^2)-1)	(alpha/E) - alpha		
Health states							
Well	Beta	1	-	-	-		NICE CG181
(Post) stable angina		0.808	0.038	86.00	20.44		
Unstable angina		0.770	0.038	93.67	27.98		
Post-unstable angina		0.880	0.018	285.93	38.99		
MI		0.760	0.018	427.09	134.87		
Post-MI		0.880	0.018	285.93	38.99		
TIA/post-TIA		0.900	0.025	128.70	14.30		
Stroke/post-stroke		0.628	0.040	91.07	53.94		
Dead states		0	-	-	-		
FH-associated relative risk CHD			**LL 95% CI**	**UL 95% CI**	**Ln(mean)**	**Ln(SE)**	
<39 years	Log-normal	84.3	33.8	173.3	4.43	0.42	(SB Register Group, 1991)
40-59 years		5.3	2.7	9.2	1.67	0.31	
Relative risk of outcome per mM LDL-C reduction							
Non-fatal CHD	Log-normal	0.74	0.69	0.78	-0.30	0.03	(CTT, 2010)
Ischaemic stroke		0.8	0.73	0.88	-0.22	0.05	
Fatal CHD		0.8	0.73	0.86	-0.22	0.04	
Pre-treatment LDL-C (mM)			**LL 95% CI**	**UL 95% CI**	**SE**		
0 -19 years	Normal[b]	5.82	5.56	6.08	0.13		(Kerr et al., 2017)
20-24 years		6.36	5.54	7.18	0.42		
25-34 years		6.9	6.45	7.35	0.23		
35-44 years		7.51	6.88	8.15	0.32		
45-54 years		7.57	6.71	8.42	0.44		
55+ years		8.3	7.35	9.25	0.48		

Supplementary File 6: Familial hypercholesterolaemia case yields and costs per diagnosis under each screening strategy, as modelled in deterministic sensitivity analyses

Results are presented for all scenarios where screening outcomes differ from the base case scenario

US: universal screening; RCT: reverse cascade testing

a. DSA adjustment: All M+ defined as FH+

	FH cases identified per 10,000 screened in US			Screening costs per diagnosis (£)		
	US	RCT	total	US	RCT	total
No screening	0	0	0	n/a	n/a	n/a
Cholesterol-only screening	22.38	0	22.38	11,788	n/a	11,788
Sequential genetic-cholesterol screening	14.05	0	14.05	176,742	n/a	176,742
Sequential cholesterol-genetic screening	24.41	0	24.41	13,785	n/a	13,785
Parallel cholesterol-genetic screening	28.04	0	28.04	89,751	n/a	89,751
Sequential genetic-cholesterol screening plus RCT	14.05	28.10	42.15	176,742	777	59,432
Sequential cholesterol-genetic screening plus RCT	24.41	21.97	46.38	13,785	777	7,624
Parallel cholesterol-genetic screening plus RCT	28.04	28.10	56.14	89,751	777	45,212

b. DSA adjustment: RCT case yield/index = 0.5

	FH cases identified per 10,000 screened			Screening costs per diagnosis (£)		
	US	RCT	total	US	RCT	total
No screening	0	0	0	n/a	n/a	n/a
Cholesterol-only screening	22.38	0	22.38	11,788	n/a	11,788
Sequential genetic-cholesterol screening	11.44	0	11.44	217,036	n/a	217,036
Sequential cholesterol-genetic screening	24.41	0	24.41	13,785	n/a	13,785
Parallel cholesterol-genetic screening	25.43	0	25.43	98,959	n/a	98,959
Sequential genetic-cholesterol screening plus RCT	11.44	4.92	16.36	217,036	1,165	152,146
Sequential cholesterol-genetic screening plus RCT	24.41	3.84	28.26	13,785	1,165	12,068
Parallel cholesterol-genetic screening plus RCT	25.43	4.92	30.35	98,959	1,165	83,110

c. DSA adjustment: RCT case yield/index = 6.1

	FH cases identified per 10,000 screened			Screening costs per diagnosis (£)		
	US	RCT	total	US	RCT	total
No screening	0	0	0	n/a	n/a	n/a
Cholesterol-only screening	22.38	0	22.38	11,788	n/a	11,788
Sequential genetic-cholesterol screening	11.44	0	11.44	217,036	n/a	217,036
Sequential cholesterol-genetic screening	24.41	0	24.41	13,785	n/a	13,785
Parallel cholesterol-genetic screening	25.43	0	25.43	98,959	n/a	98,959
Sequential genetic-cholesterol screening plus RCT	11.44	60.00	71.44	217,036	1,098	35,684
Sequential cholesterol-genetic screening plus RCT	24.41	46.91	71.32	13,785	1,098	5,441
Parallel cholesterol-genetic screening plus RCT	25.43	60.00	85.43	98,959	1,098	30,227

d. DSA adjustment: RCT case yield/index = 8.6; probability relative M+ = 0.31

	FH cases identified per 10,000 screened in US			Screening costs per diagnosis (£)		
	US	RCT	total	US	RCT	total
No screening	0	0	0	n/a	n/a	n/a
Cholesterol-only screening	22.38	0	22.38	11,788	n/a	11,788
Sequential genetic-cholesterol screening	11.44	0	11.44	217,036	n/a	217,036
Sequential cholesterol-genetic screening	24.41	0	24.41	13,785	n/a	13,785
Parallel cholesterol-genetic screening	25.43	0	25.43	98,959	n/a	98,959
Sequential genetic-cholesterol screening plus RCT	11.44	84.59	96.03	217,036	1,414	27,106
Sequential cholesterol-genetic screening plus RCT	24.41	66.13	90.54	13,785	1,414	4,749
Parallel cholesterol-genetic screening plus RCT	25.43	84.59	110.02	98,959	1,414	23,959

e. DSA adjustment: RCT case yield/index = 8.6; probability relative M+ = 0.21

	FH cases identified per 10,000 screened in US			Screening costs per diagnosis (£)		
	US	RCT	total	US	RCT	total
No screening	0	0	0	n/a	n/a	n/a
Cholesterol-only screening	22.38	0	22.38	11,788	n/a	11,788
Sequential genetic-cholesterol screening	11.44	0	11.44	217,036	n/a	217,036
Sequential cholesterol-genetic screening	24.41	0	24.41	13,785	n/a	13,785
Parallel cholesterol-genetic screening	25.43	0	25.43	98,959	n/a	98,959
Sequential genetic-cholesterol screening plus RCT	11.44	84.59	96.03	217,036	2.049	27,666
Sequential cholesterol-genetic screening plus RCT	24.41	66.13	90.54	13,785	2.049	5,213
Parallel cholesterol-genetic screening plus RCT	25.43	84.59	110.02	98,959	2.049	24,448

f. DSA adjustment: Cholesterol test true positive rate for sequential cholesterol-genetic US strategy = 62.5%
*NB. Cholesterol-only cholesterol threshold not adjusted in DSA as not clear that performance would be acceptable even using thresholds of highest described post-test probability (=0.53) in recent analysis, and not of concern as strategy dominated even at base case performance for this strategy (see Supplementary File 7, Table r)

	FH cases identified per 10,000 screened in US			Screening costs per diagnosis (£)		
	US	RCT	total	US	RCT	total
No screening	0	0	0	n/a	n/a	n/a
Cholesterol-only screening*	22.38	0	22.38	11,788	n/a	11,788
Sequential genetic-cholesterol screening	11.44	0	11.44	217,036	n/a	217,036
Sequential cholesterol-genetic screening	15.89	0	15.89	21,023	n/a	21,023
Parallel cholesterol-genetic screening	25.43	0	25.43	98,959	n/a	98,959
Sequential genetic-cholesterol screening plus RCT	11.44	19.67	31.11	217,036	1,110	80,519
Sequential cholesterol-genetic screening plus RCT	15.89	10.01	25.90	21,023	1,110	13,327
Parallel cholesterol-genetic screening plus RCT	25.43	19.67	45.10	98,959	1,110	56,279

g. DSA adjustment: Universal screening appointment duration = 40 minutes

	FH cases identified per 10,000 screened in US			Screening costs per diagnosis (£)		
	US	RCT	total	US	RCT	total
No screening	0	0	0	n/a	n/a	n/a
Cholesterol-only screening	22.38	0	22.38	14,127	n/a	14,127
Sequential genetic-cholesterol screening	11.44	0	11.44	221,611	n/a	221,611
Sequential cholesterol-genetic screening	24.41	0	24.41	15,930	n/a	15,930
Parallel cholesterol-genetic screening	25.43	0	25.43	101,018	n/a	101,018
Sequential genetic-cholesterol screening plus RCT	11.44	19.67	31.11	221,611	1,110	82,201
Sequential cholesterol-genetic screening plus RCT	24.41	15.38	39.79	15,930	1,110	10,202
Parallel cholesterol-genetic screening plus RCT	25.43	19.67	45.10	101,018	1,110	57,439

Supplementary File 7: Deterministic sensitivity analysis incremental cost effectiveness ratio comparisons

QALY: quality adjusted life year; ICER: incremental cost-effectiveness ratio; RCT: reverse cascade testing; SD: strongly dominated

a. DSA adjustment: Costs for treatment of false positives included

			ICER (£/QALY)		
	QALYs	**Costs (£)**	**versus no screening**	**versus next lowest cost**	**versus relevant alternative**
No screening	991.8	225,983	-	-	-
Cholesterol-only screening	1,009.2	601,172	21,608	21,608	ED
Sequential cholesterol-genetic screening	1,010.7	640,288	21,872	24,781	ED
Sequential cholesterol-genetic screening plus RCT	1,027.5	672,362	12,480	1,906	12,480
Sequential genetic-cholesterol screening	1,000.7	2,745,892	283,799	SD	SD
Sequential genetic-cholesterol screening plus RCT	1,022.2	2,786,918	84,240	SD	SD
Parallel cholesterol-genetic screening	1,011.5	2,823,343	131,635	SD	SD
Parallel cholesterol-genetic screening plus RCT	1,033.0	2,864,370	63,957	399,581	399,581

b. DSA adjustment: All M+ defined as FH+

			ICER (£/QALY)		
	QALYs	**Costs (£)**	**versus no screening**	**versus next lowest cost**	**versus relevant alternative**
No screening	1,213.0	289,459	-	-	-
Cholesterol-only screening	1,229.6	626,726	20,311	20,311	ED
Sequential cholesterol-genetic screening	1,231.1	706,141	23,003	52,609	ED
Sequential cholesterol-genetic screening plus RCT	1,254.2	747,363	11,111	1,785	11,111
Sequential genetic-cholesterol screening	1,223.4	2,819,049	242,603	SD	SD
Sequential genetic-cholesterol screening plus RCT	1,252.9	2,871,778	64,607	SD	SD
Parallel cholesterol-genetic screening	1,233.8	2,897,862	125,374	SD	SD
Parallel cholesterol-genetic screening plus RCT	1,263.3	2,950,591	52,855	241,117	241,117

c. DSA adjustment: RCT case yield/index = 0.5

			ICER (£/QALY)		
	QALYs	**Costs (£)**	**versus no screening**	**versus next lowest cost**	**versus relevant alternative**
No screening	715.0	136,062	-	-	-
Cholesterol-only screening	732.3	471,151	19,298	19,298	ED
Sequential cholesterol-genetic screening	733.9	550,368	21,872	50,184	ED
Sequential cholesterol-genetic screening plus RCT	738.1	558,597	18,253	1,956	18,253
Sequential genetic-cholesterol screening	723.9	2,655,971	283,799	SD	SD
Sequential genetic-cholesterol screening plus RCT	729.2	2,666,498	177,456	SD	SD
Parallel cholesterol-genetic screening	734.7	2,733,423	131,635	SD	SD
Parallel cholesterol-genetic screening plus RCT	740.1	2,743,949	103,851	1,113,050	1,113,050

d. DSA adjustment: RCT case yield/index = 6.1

			ICER (£/QALY)		
	QALYs	**Costs (£)**	**versus no screening**	**versus next lowest cost**	**versus relevant alternative**
No screening	1,748.4	471,765	-	-	-
Cholesterol-only screening	1,765.7	806,854	19,298	19,298	ED
Sequential cholesterol-genetic screening	1,767.3	886,071	21,872	50,184	ED
Sequential cholesterol-genetic screening plus RCT	1,818.6	983,318	7,281	1,895	7,281
Sequential genetic-cholesterol screening	1,757.2	2,991,674	283,799	SD	SD
Parallel cholesterol-genetic screening	1,768.1	3,069,125	131,635	SD	SD
Sequential genetic-cholesterol screening plus RCT	1,822.9	3,116,067	35,485	500,499	ED
Parallel cholesterol-genetic screening plus RCT	1,833.7	3,193,519	31,881	7,137	146,239

e. DSA adjustment: RCT case yield/index = 8.6; probability relative M+ = 0.31

			ICER (£/QALY)		
	QALYs	**Costs (£)**	**versus no screening**	**versus next lowest cost**	**versus relevant alternative**
No screening	2,209.7	621,632	-	-	-
Cholesterol-only screening	2,227.1	956,721	19,298	19,298	ED
Sequential cholesterol-genetic screening	2,228.7	1,035,938	21,872	50,184	ED
Sequential cholesterol-genetic screening plus RCT	2,301.0	1,193,919	6,269	2,184	6,269
Sequential genetic-cholesterol screening	2,218.6	3,141,541	283,799	SD	SD
Parallel cholesterol-genetic screening	2,229.4	3,218,993	131,635	SD	SD
Sequential genetic-cholesterol screening plus RCT	2,311.1	3,343,622	26,839	212,172	ED
Parallel cholesterol-genetic screening plus RCT	2,322.0	3,421,074	24,934	7,137	106,135

f. DSA adjustment: RCT case yield/index = 8.6; probability relative M+ = 0.21

			ICER (£/QALY)		
	QALYs	**Costs (£)**	**versus no screening**	**versus next lowest cost**	**versus relevant alternative**
No screening	2,209.7	621,632	-	-	-
Cholesterol-only screening	2,227.1	956,721	19,298	19,298	ED
Sequential cholesterol-genetic screening	2,228.7	1,035,938	21,872	50,184	ED
Sequential cholesterol-genetic screening plus RCT	2,301.0	1,235,907	6,729	2,764	6,729
Sequential genetic-cholesterol screening	2,218.6	3,141,541	283,799	SD	SD
Parallel cholesterol-genetic screening	2,229.4	3,218,993	131,635	SD	SD
Sequential genetic-cholesterol screening plus RCT	2,311.1	3,397,331	27,368	213,329	ED
Parallel cholesterol-genetic screening plus RCT	2,322.0	3,474,782	25,413	7,137	106,693

g. DSA adjustment: 100% of diagnosed adults treated

			ICER (£/QALY)		
	QALYs	**Costs (£)**	**versus no screening**	**versus next lowest cost**	**versus relevant alternative**
No screening	991.8	225,983	-	-	
Cholesterol-only screening	1,012.0	565,780	16,776	16,776	ED
Sequential cholesterol-genetic screening	1,013.9	645,425	18,982	43,253	ED
Sequential cholesterol-genetic screening plus RCT	1,033.6	679,495	10,832	1,723	10,832
Sequential genetic-cholesterol screening	1,002.1	2,748,299	243,521	SD	SD
Sequential genetic-cholesterol screening plus RCT	1,027.4	2,791,880	71,981	SD	SD
Parallel cholesterol-genetic screening	1,014.8	2,828,694	113,077	SD	SD
Parallel cholesterol-genetic screening plus RCT	1,040.1	2,872,274	54,782	340,523	340,523

h. DSA adjustment: 100% of diagnosed treated from 8 years

			ICER (£/QALY)		
	QALYs	**Costs (£)**	**versus no screening**	**versus next lowest cost**	**versus relevant alternative**
No screening	991.8	225,983	-	-	-
Cholesterol-only screening	1,012.8	566,626	16,209	16,209	ED
Sequential cholesterol-genetic screening	1,014.7	646,348	18,335	41,727	ED
Sequential cholesterol-genetic screening plus RCT	1,034.6	680,443	10,619	1,716	10,619
Sequential genetic-cholesterol screening	1,002.5	2,748,732	234,744	SD	SD
Sequential genetic-cholesterol screening plus RCT	1,027.9	2,792,344	70,963	SD	SD
Parallel cholesterol-genetic screening	1,015.7	2,829,655	109,023	SD	SD
Parallel cholesterol-genetic screening plus RCT	1,041.1	2,873,268	53,698	337,246	337,246

i. DSA adjustment: 15% discontinue LMT at 10 years

			ICER (£/QALY)		
	QALYs	Costs (£)	versus no screening	versus next lowest cost	versus relevant alternative
No screening	991.8	225,983	-	-	-
Cholesterol-only screening	1,006.8	558,312	22,177	22,177	ED
Sequential cholesterol-genetic screening	1,008.1	637,278	25,159	57,965	ED
Sequential cholesterol-genetic screening plus RCT	1,023.6	668,645	13,927	2,032	13,927
Sequential genetic-cholesterol screening	999.4	2,744,480	328,656	SD	SD
Sequential genetic-cholesterol screening plus RCT	1,019.2	2,784,604	93,347	SD	SD
Parallel cholesterol-genetic screening	1,008.8	2,820,207	152,342	SD	SD
Parallel cholesterol-genetic screening plus RCT	1,028.6	2,860,331	71,633	439,178	439,178

j. DSA adjustment: 50% LDL-C reduction achieved with LMT

			ICER (£/QALY)		
	QALYs	Costs (£)	versus no screening	versus next lowest cost	versus relevant alternative
No screening	992.5	224,945	-	-	-
Cholesterol-only screening	1,018.1	538,673	12,272	12,272	ED
Sequential cholesterol-genetic screening	1,020.4	615,958	14,020	33,249	ED
Sequential cholesterol-genetic screening plus RCT	1,044.7	628,769	7,733	527	7,733
Sequential genetic-cholesterol screening	1,005.6	2,733,931	191,917	SD	SD
Sequential genetic-cholesterol screening plus RCT	1,036.7	2,750,330	57,140	SD	SD
Parallel cholesterol-genetic screening	1,021.6	2,798,032	88,569	SD	SD
Parallel cholesterol-genetic screening plus RCT	1,052.7	2,814,431	43,032	274,785	274,785

k. DSA adjustment: Estimated off-patent LMT costs applied

			ICER (£/QALY)		
	QALYs	**Costs (£)**	**versus no screening**	**versus next lowest cost**	**versus relevant alternative**
No screening	992.8	224,417	-	-	
Cholesterol-only screening	1,009.8	519,575	17,276	17,276	ED
Sequential cholesterol-genetic screening	1,011.4	595,162	19,892	48,666	ED
Sequential cholesterol-genetic screening plus RCT	1,028.0	597,766	10,600	157	10,600
Sequential genetic-cholesterol screening	1,001.5	2,723,907	286,093	SD	SD
Sequential genetic-cholesterol screening plus RCT	1,022.7	2,727,237	83,569	SD	SD
Parallel cholesterol-genetic screening	1,012.2	2,776,402	131,446	SD	SD
Parallel cholesterol-genetic screening plus RCT	1,033.4	2,779,732	62,897	403,638	403,638

l. DSA adjustment: Discount rate = 1.5%

			ICER (£/QALY)		
	QALYs	**Costs (£)**	**versus no screening**	**versus next lowest cost**	**versus relevant alternative**
No screening	1,552.0	458,095	-	-	-
Cholesterol-only screening	1,600.9	809,893	7,193	7,193	ED
Sequential cholesterol-genetic screening	1,605.4	890,629	8,107	18,158	ED
Sequential cholesterol-genetic screening plus RCT	1,636.4	921,203	5,489	986	5,489
Sequential genetic-cholesterol screening	1,577.0	2,986,548	101,097	SD	SD
Sequential genetic-cholesterol screening plus RCT	1,616.7	3,025,657	39,696	SD	SD
Parallel cholesterol-genetic screening	1,607.6	3,074,443	47,075	SD	SD
Parallel cholesterol-genetic screening plus RCT	1,647.2	3,113,552	27,879	201,494	201,494

m. DSA adjustment: Discount rate = 5.0%

			ICER (£/QALY)		
	QALYs	**Costs (£)**	**versus no screening**	**versus next lowest cost**	**versus relevant alternative**
No screening	765.6	145,745	-	-	-
Cholesterol-only screening	774.2	469,146	37,804	37,804	ED
Sequential cholesterol-genetic screening	774.9	547,300	43,028	100,495	ED
Sequential cholesterol-genetic screening plus RCT	786.4	578,782	20,849	2,752	20,849
Sequential genetic-cholesterol screening	770.0	2,659,677	574,675	SD	SD
Sequential genetic-cholesterol screening plus RCT	784.6	2,699,946	134,393	SD	SD
Parallel cholesterol-genetic screening	775.3	2,729,824	265,820	SD	SD
Parallel cholesterol-genetic screening plus RCT	789.9	2,770,093	107,767	611,804	611,804

n. DSA adjustment: CVD risks 90% of base case estimates

			ICER (£/QALY)		
	QALYs	**Costs (£)**	**versus no screening**	**versus next lowest cost**	**versus relevant alternative**
No screening	1,002.0	210,053	-	-	-
Cholesterol-only screening	1,018.2	547,356	20,845	20,845	ED
Sequential cholesterol-genetic screening	1,019.7	626,774	23,607	53,989	ED
Sequential cholesterol-genetic screening plus RCT	1,035.2	661,346	13,609	2,229	13,609
Sequential genetic-cholesterol screening	1,010.3	2,731,094	304,677	SD	SD
Sequential genetic-cholesterol screening plus RCT	1,030.1	2,775,317	91,252	SD	SD
Parallel cholesterol-genetic screening	1,020.4	2,809,929	141,392	SD	SD
Parallel cholesterol-genetic screening plus RCT	1,040.2	2,854,152	69,172	432,969	432,969

o. DSA adjustment: CVD risks 80% of base case estimates

			ICER (£/QALY)		
	QALYs	**Costs (£)**	**versus no screening**	**versus next lowest cost**	**versus relevant alternative**
No screening	1,011.3	195,509	-	-	-
Cholesterol-only screening	1,026.3	535,227	22,724	22,724	ED
Sequential cholesterol-genetic screening	1,027.6	614,865	25,713	58,597	ED
Sequential cholesterol-genetic screening plus RCT	1,041.9	651,892	14,941	2,601	14,941
Sequential genetic-cholesterol screening	1,019.0	2,717,785	329,930	SD	SD
Sequential genetic-cholesterol screening plus RCT	1,037.2	2,765,147	99,381	SD	SD
Parallel cholesterol-genetic screening	1,028.3	2,798,130	153,198	SD	SD
Parallel cholesterol-genetic screening plus RCT	1,046.5	2,845,493	75,283	471,355	471,355

p. DSA adjustment: Undiagnosed cases treated at background rate

			ICER (£/QALY)		
	QALYs	**Costs (£)**	**versus no screening**	**versus next lowest cost**	**versus relevant alternative**
No screening	1,009.1	265,734	-	-	-
Cholesterol-only screening	1,022.4	587,115	24,174	24,174	ED
Sequential cholesterol-genetic screening	1,023.6	665,086	27,536	64,514	ED
Sequential cholesterol-genetic screening plus RCT	1,035.4	685,867	15,966	1,760	15,966
Sequential genetic-cholesterol screening	1,015.9	2,778,633	369,636	SD	SD
Sequential genetic-cholesterol screening plus RCT	1,031.0	2,805,215	115,928	SD	SD
Parallel cholesterol-genetic screening	1,024.2	2,847,517	170,896	SD	SD
Parallel cholesterol-genetic screening plus RCT	1,039.3	2,874,099	86,327	560,918	560,918

q. DSA adjustment: Cholesterol test true positive rate for sequential cholesterol-genetic US strategy = 62.5%
*NB. Cholesterol-only cholesterol threshold not adjusted in DSA as not clear that performance would be acceptable even using thresholds of highest described post-test probability (=0.53) in recent analysis, and not of concern as strategy dominated even at base case performance for this strategy

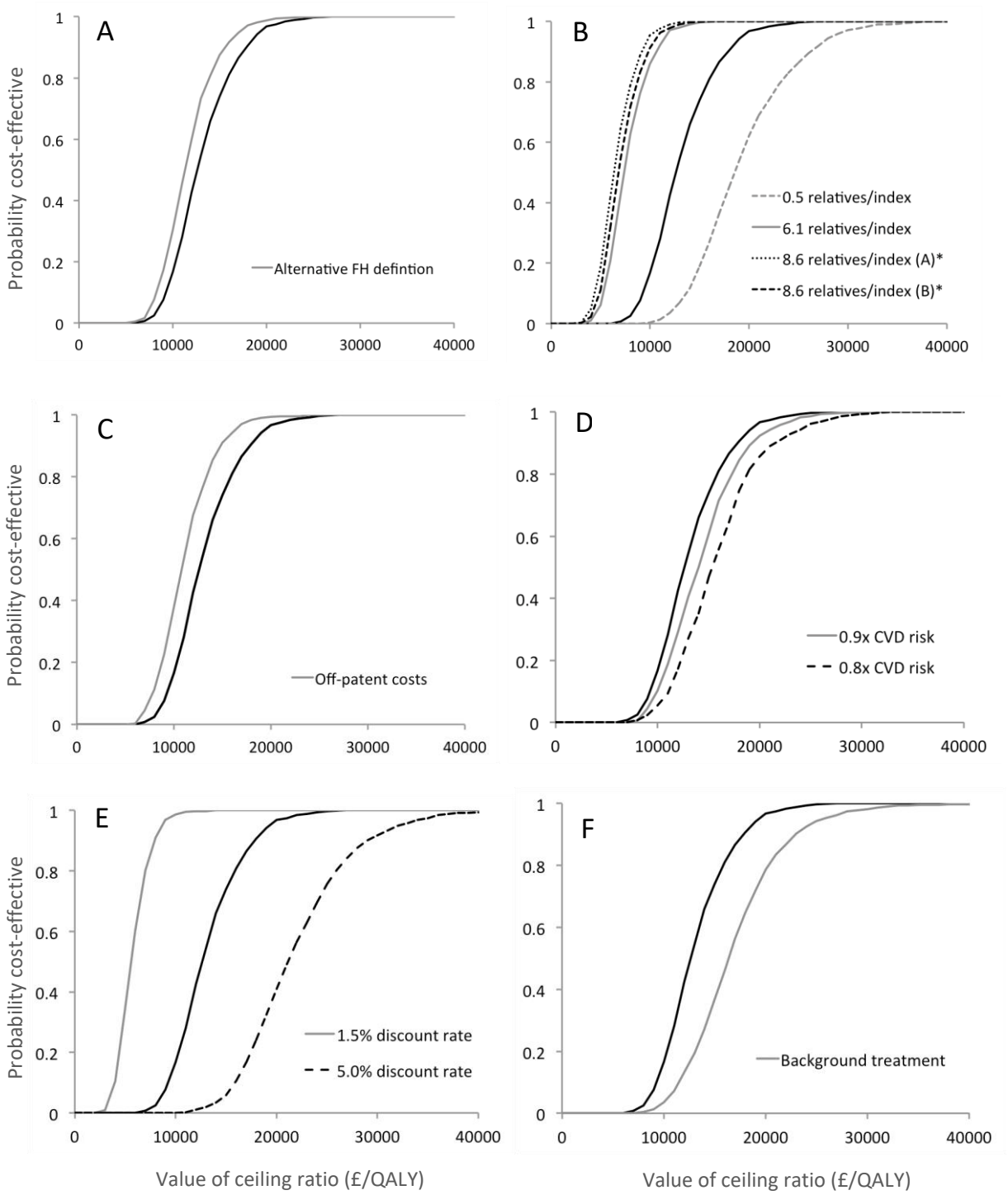
			ICER (£/QALY)		
	QALYs	**Costs (£)**	**versus no screening**	**versus next lowest cost**	**versus relevant alternative**
No screening	992.1	225,805	-	-	-
Cholesterol-only screening*	1,009.5	560,648	19,218	19,218	ED
Sequential cholesterol-genetic screening	1,004.5	610,384	31,078	SD	SD
Sequential cholesterol-genetic screening plus RCT	1,015.5	631,138	17,350	11,870	17,350
Sequential genetic-cholesterol screening	1,001.0	2,745,588	282,813	SD	SD
Sequential genetic-cholesterol screening plus RCT	1,022.6	2,786,366	83,960	302,049	SD
Parallel cholesterol-genetic screening	1,011.9	2,822,886	131,170	SD	SD
Parallel cholesterol-genetic screening plus RCT	1,033.5	2,863,664	63,736	7,098	123,857

r. DSA adjustment: Universal screening appointment duration = 40 minutes

			ICER (£/QALY)		
	QALYs	**Costs (£)**	**versus no screening**	**versus next lowest cost**	**versus relevant alternative**
No screening	991.9	226,236	-	-	-
Cholesterol-only screening	1009.3	613,460	22,244	22,244	ED
Sequential cholesterol-genetic screening	1010.9	692,658	24,561	50,045	ED
Sequential cholesterol-genetic screening plus RCT	1027.7	724,573	13,902	1,894	13,902
Sequential genetic-cholesterol screening	1000.8	2,798,384	288,946	SD	SD
Sequential genetic-cholesterol screening plus RCT	1022.3	2,839,209	85,779	SD	SD
Parallel cholesterol-genetic screening	1011.6	2,875,703	133,934	SD	SD
Parallel cholesterol-genetic screening plus RCT	1033.2	2,916,527	65,074	398,808	398,808

Supplementary File 8: Cost-effectiveness acceptability curves

Probability of cost-effectiveness of sequential cholesterol-genetic plus reverse cascade testing (RCT) versus no screening is displayed for the base case (black line) and deterministic sensitivity analysis scenarios that modelled a definition of familial hypercholesterolaemia that included all mutation-positive individuals (A), different RCT yields (B), off-patent drug costs (C), lower cardiovascular (CVD) risk estimates (D), alternative discount rates (E) and background lipid modifying treatment (F); *A: 6.1 relatives identified with probability = 0.4; 2.5 with probability = 0.2; B: 6.1 identified with probability = 0.4; 2.5 with probability = 0.1



Supplementary File 9: Additional references

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