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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Supplementary files 9

> **Commented [MAJ1]:** Max 3500

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.

Funding None

> **Commented [DM2]:** I wonder whether this is too technical for general audience?
>
> Is the results main message focusing on technical details of the preferred option, or comparison with other strategies?

> **Commented [MAJ3]:** Do you think ok to leave this? I think the probability of CEs is useful, and probably even if unfamiliar with the type of analysis someone would get the idea?
>
> We haven't done any analyses relating to the technicalities of the strategy as such, so I think the comparisons are the main/only results i.e. CE or not, but I may have misunderstood the question?

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.

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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

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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 2 would result in some individuals being partially tested against standard UK diagnostic criteria and at risk of false positive results

Commented [am4]: Does this mean these options should be in theory be other arms in your evaluation. I'm not quite sure how this approach fits into the picture or how it overlaps with the treatment options evaluated herein. The age groups seem to overlap?

Commented [MAJ5R4]: I've tried to add some info to explain. Hope it might help?

Commented [am6]: Just so I'm clear wrt to the box. No screening is the same as saying 'CT alone' ie when an index appears unprompted as it were?

Commented [MAJ7R6]: Yes – have added a note

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

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Commented [DM8]: Does this mean that only those with identified mutation were subject to RCT?

Commented [MAJ9R8]: everyone with a mutation (whether they had a base case FH Dx or not), and only individuals with mutations (whether they had a base case FH Dx or not)

Commented [am10]: Is this the number of PSA runs? If so its better to state it as so.

Commented [MAJ11R10]: It's the number of 1-2 yr olds in each cohort

Commented [DM12]: Should this come third, to match Box 1 order?

Commented [MAJ13R12]: This is about the model structure, whereas Box 1 about the alternatives modelled. In the models, we need to ID everyone we're going to ID before estimating their outcomes in MMs.

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 2 years, 5 years, and each subsequent 5-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

Commented [am14]: I'm lost with some of the medical detail here, but assume it means something to people in the know?

Commented [MAJ15R14]: Sorry Alec. This just means we expect the mutations would be inherited as per standard genetic 'rules'. Do you think it's ok to retain? It saves having to say we expect X, Y, Z probabilities of inheritance depending on how far relatives are removed from the index case, and explaining why… I would expect universal understanding among medics and anyone else with school/UG-level biology, but realise this isn't everyone…

Commented [am16]: Above it says 10,000

Commented [MAJ17R16]: The 10,000 was the number of 1-2 yr olds in decision tree. The 1,000 is number in each MM (which doesn't relate to any cohort specifically – I combined the MM outcomes at the end according to the numbers in each cohort with each MM start age)

Commented [am18]: It might not be relevant here, but I'm unclear how you included the CT component? Or have I misunderstood something?

Commented [MAJ19R18]: It is relevant – sorry, I meant to explain in the previous paragraph, but obviously didn't successfully… Essentially, I added (to the number of infants identified in US) the number of people we (currently in the UK) on average identify in CT from each index case (adj for things like mutation +ve vs hypercholesterolaemic), for the number of index cases identified in each cohort of n=10,000 1-2 years olds exposed to US. I've tried to re-word above, but not sure whether it helps?

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

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Comments in margin:

Commented [am20]: More usual to use a health care specific index

http://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2016/

Commented [AM21]: I've had a look at this, but still only available to 2016-17, and as CPI is more up-to-date (and higher), I thought I might go with that to be safer? (The only thing this applies to is the health state costs)

…I've taken the comment out of here and noted in table where costs listed, so could explain a bit more.

Commented [DM22]: Pretty detailed for general audience?

Commented [MAJ23R22]: I think some people would expect to see the basic info re distributions. All the details are in SF.

Commented [DM24]: Only for 2nd alternative or all?

Commented [MAJ25R24]: only relevant to second, (as per Box 1)

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).

Commented [DM26]: Don't understand this – can you just delete latter half of this sentence because you've stated headline?

Commented [MAJ27R26]: It suggests there isn't anything *additional* to the sequential chol-genetic+RCT screening method that would be cost-effective (i.e. we couldn't cost-effectively obtain more QALYs with another approach) (also see comment below)

Commented [DM28]: I wonder whether reporting each alternative model at a time might be easier to follow rather than under each Diagnosis/Cost/ICER say what highest/lowest is? So potentially expand on main results and less emphasis on DSAs?

Commented [MAJ29R28]: The numbers are in the tables, and perhaps are not of as much interest as the DSAs. I don't think the costs of the alternatives that are not the most cost-effective options are of too much concern, whereas understanding whether the same alternative is the most CE within the bounds of reasonable assumptions, and whether it is still CE under less likely but perhaps feasible constraints is important ??

Commented [DM30]: Struggling to follow

Commented [MAJ31R30]: ICER for comparison between the only strategy not dominated by 'most CE strategy vs no screening' and the most CE strategy i.e. 'additionally' screening via this other method not CE

Commented [DM32]: Too detailed for main paper results?

Commented [MAJ33R32]: Would have to take something else out?

Commented [DM34]: Hard for general audience?

Commented [MAJ35R34]: I'm not sure, but I think of interest for people that would be wondering and anyone else would guess the right idea

Commented [DM36]: Feels like reporting of DSAs getting as much 'space' as main results.

Commented [MAJ37R36]: These are not DSAs. These are results for scenarios of undiagnosed FH prevalences that could be reached if US was successfully implemented (the different values referring to scenarios with different CT approaches) The base case and DSAs assume current undiagnosed prevalence. I thought may be worth including off-patent costs here as would take some time for any US to actually meaningfully reduce prevalence (so these probably more relevant than base case costs here)

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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

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£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. and a 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. a longer period of LMT and monitoring needs to occur before there is economic benefit from avoided events. The advantage of US in childhood is that families with FH are found at an early stage of atherosclerosis development, when maximum benefit can still obtained via lifestyle and pharmacological management.

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 thresholds,[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.

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.

Conflicts of interest

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.

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