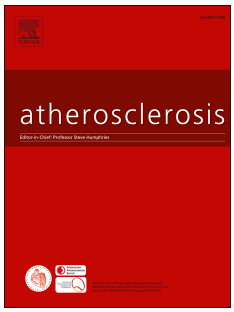
Accepted Manuscript



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

Ailsa J. McKay, Helen Hogan, Steve E. Humphries, Dalya Marks, Kausik K. Ray, Alec Miners

PII: S0021-9150(18)30290-9

DOI: 10.1016/j.atherosclerosis.2018.05.047

Reference: ATH 15542

To appear in: *Atherosclerosis*

Received Date: 4 May 2018

Revised Date: 25 May 2018

Accepted Date: 30 May 2018

Please cite this article as: McKay AJ, Hogan H, Humphries SE, Marks D, Ray KK, Miners A, Universal screening at age 1–2 years as an adjunct to cascade testing for familial hypercholesterolaemia in the UK: A cost-utility analysis, *Atherosclerosis* (2018), doi: 10.1016/j.atherosclerosis.2018.05.047.

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

Ailsa J McKay[a,b], Helen Hogan[c], Steve E Humphries[d], Dalya Marks[e], Kausik K Ray[b], Alec Miners[c]

a. London School of Hygiene and Tropical Medicine, London, UK

b. Department of Primary Care and Public Health, Imperial College London, London, UK

c. Department of Health Services Research and Policy, London School of Hygiene and Tropical Medicine, London, UK

d. Cardiovascular Genetics, Institute of Cardiovascular Science, University College London, London, UK

e. Department of Public Health, Environments and Society, London School of Hygiene and Tropical Medicine, London, UK

Corresponding author Ailsa McKay, ailsa.mckay08@imperial.ac.uk

Abstract

Background and aims: Familial hypercholesterolaemia (FH) is widely underdiagnosed. Cascade testing (CT) of relatives has been shown to be feasible, acceptable and cost-effective in the UK, but requires 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 healthcare 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.

Results: A strategy involving cholesterol screening followed by diagnostic genetic testing and RCT was the most cost-effective modelled (incremental cost-effectiveness ratio (ICER) *versus* no US £12,480/quality adjusted life year (QALY); probability of cost-effectiveness 96·8% at £20,000/QALY threshold). Cost-effectiveness was robust to both deterministic sensitivity analyses and threshold analyses that modelled ongoing case ascertainment at theoretical maximum levels.

Conclusions: 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.

Key words Hyperlipoproteinaemia type II, systematic population screening, cost-effectiveness

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

Materials and 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 (personal communication).[17] 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 28] 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] and that 70% of RCT-identified mutation-positive relatives would meet the base case FH definition.[29-31] 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 32] Briefly, baseline CVD risks drew on the QRISK2 model,[33] 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.[34] 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,[32] 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,[35 36] 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 37] 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).[37] 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).[38] The CTT values were assumed applicable to both primary and secondary events.

Cycle health state outcomes were weighted with the utilities described in CG181,[32] 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,[39 40] 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 28] 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),[41] 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.[42] 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.[42] 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.[24,43] 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.[44]

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,[45] and recent local data were available to estimate several parameters.

The persistent uncertainty around the sensitivity and specificity of different cholesterol theresholds,[46] although considered in DSA (where we modelled the proportion of those with FH with cholesterol levels exceeding the threshold for genetic testing down to 62.5%) , is an important limitation of all work in this area, and sensitive to the definition of FH applied. 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, as well as 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). As practical and ethical issues impact ability to overcome some of these limitations, assumptions are necessary if a decision is to be made on the basis of all information that *is* available. Although the assumptions will impact on accuracy, several are common to previous models used in UK healthcare decision-making (e.g. the HTA for lipid modification in prevention of CVD, and the HTA that led to introduction of cluster testing for FH). The assumptions applied may therefore be reasonable to UK healthcare decision-makers, and accuracy is potentially less of a concern if conservative assumptions lead to outcomes below a fixed willingness-to-pay threshold, as in this case.

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.[47 48] The models also assumed no pre-existing CVD, which will not always be the case.[49] 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. Regarding generalisability, economic evaluations require analyses to be contextualised, and the study is therefore of most direct relevance to the UK. However, as cost-effectiveness of US has not previously been demonstrated for any setting, and cost-effectiveness in the UK is likely to be associated with cost-effectiveness elsewhere, the findings are likely to be of wider relevance, and may prompt review of the issue and analyses for non-UK contexts. Under-diagnosis is a global concern, and universal screening is currently implemented, recommended and/or under consideration by relevant bodies in various jurisdictions.[50-53]

Implications for research and practice

2016 UK 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.[54] 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.[39 55-57] 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.

Our analyses focused on screening at age 1-2 years, in view of recently demonstrated feasibility for this age-group. Whilst this may be considered an appropriate age for screening in some contexts, others have shown interest in screening school-age children.[50-53] The economic implications of screening at slightly higher ages are likely to be minimal, and screening at such ages could again be linked to other routine childhood healthcare attendances. Vaccination uptake rates indicate that this would be unlikely to have a major impact on screening participation, at least in the UK. A key issue for decisions about optimal

screening age is the outstanding uncertainty around the optimal age for treatment initiation. It remains possible this may be around the time of school entry, or earlier.[58] Once better understood, screening at an age that limits the need for ongoing review during a period of limited treatment options (i.e. when LMT is not effective and/or licensed) - and the potential associated anxiety – may be preferred. It has also been suggest that screening would be best achieved whilst the sensitivity and specificity of cholesterol testing remains optimal.[50]

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.

Conflict of interest

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.

Financial support

SEH acknowledges support from the British Heart Foundation (BHF) (BHF PG08/008) and the NIHR UCLH BRC.

Author contributions

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.

Ethics statement

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

References

1. Brown MS, Goldstein JL. A receptor-mediated pathway for cholesterol homeostasis. *Science* 1986;**232**:34–47.
2. Benn M, Watts GF, Tybjaerg-Hansen A, Nordestgaard BG. Familial Hypercholesterolemia in the Danish General Population: Prevalence, Coronary Artery Disease, and Cholesterol-Lowering Medication. *Journal Clin Endocrinol Metab* 2012;**97**:3956–64.
3. Scientific Steering Committee on behalf of the Simon Broome Register Group. Risk of fatal coronary heart disease in familial hypercholesterolaemia. *BMJ* 1991;**303**:893–-96.
4. Goldstein JL, Hobbs HH, Brown MS. Scriver CR, Beaudet AL, et al. Familial hypercholesterolemia. The metabolic and molecular bases of inherited disease, 8th ed. New York: McGraw-Hill, 2001. (pp. 2863-2913).
5. Slack J. Risks of ischaemic heart disease in familial hyperlipoproteinaemic states. *Lancet* 1969;**294**:1380–82.
6. Stone NJ, Levy RI, Fredrickson DS,Verter J. Coronary Artery Disease in 116 Kindred with Familial Type II Hyperlipoproteinemia. *Circulation* 1974;**49**:476–88.
7. Akioyamen LE, Genest J, Shan SD, Reel RL, Albaum JM, et al. Estimating the prevalence of heterozygous familial hypercholesterolaemia: a systematic review and meta-analysis. *BMJ Open* 2017;**7**:e016461.
8. International Atherosclerosis Society Severe Familial Hypercholesterolaemia Panel. Defining severe familial hypercholesterolaemia and the implications for clinical management: a consensus statement from the International Atherosclerosis Society Severe Familial Hypercholesterolemia Panel. *Lancet Diabetes Endocrinol*. 2017;**4**:850–61.
9. European Atherosclerosis Society Consensus Panel. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. *Eur Heart J* 2013;**34**:3478–90a.
10. Pedersen KMV, Humphries SE, Roughton M, Besford JS. National Clinical Audit of the Management of Familial Hypercholesterolaemia 2010: Full Report. Clinical Standards Department, Royal College of Physicians, December 2010.
11. Ford I, Murray H, McCowan C, Packard CJ. Long-Term Safety and Efficacy of Lowering Low-Density Lipoprotein Cholesterol With Statin Therapy: 20-Year Follow-Up of West of Scotland Coronary Prevention Study. *Circulation* 2016;**133**:1073–80.
12. Braamskamp MJAM, Kastelein JJP, Kusters DM, Hutten BA, Wiegman A. Statin Initiation during Childhood in Patients with Familial Hypercholesterolemia Consequences for Cardiovascular Risk. *J Am Coll Cardiol* 2016;**67**:455–56.

13. Kusters DM, Avis HJ, de Groot E, Wijburg FA, Kastelein JJ, et al. Ten-year follow-up after initiation of statin therapy in children with familial hypercholesterolemia. *JAMA* 2014;**312**:1055–7.
14. Vuorio A, Kuoppala J, Kovanen PT, Humphries SE, Tonstad S, et al. Statins for children with familial hypercholesterolemia. *Cochrane Database Syst Rev* 2017;**7**:CD006401
15. Humphries SE, Cooper J, Dale P, Ramaswami U, FH Paediatric Register Steering Group. The UK Paediatric Familial Hypercholesterolaemia Register: Statin-related safety and 1-year growth data. *J Clin Lipidol* 2017;**12**:25–32.
16. National Institute for Health and Care Excellence. Familial hypercholesterolaemia: identification and management (CG71). NICE, 2008 (Last updated Novemeber 2017).
17. Kerr M, Pears R, Miedzybrodzka Z, Haralambos K, Cather M, et al. Cost effectiveness of cascade testing for familial hypercholesterolaemia, based on data from familial hypercholesterolaemia services in the UK. *Eur Heart J* 2017;**38**:1832–39.
18. Nherera L, Marks D, Minhas R, Thorogood M, Humphries SE. Probabilistic cost-effectiveness analysis of cascade screening for familial hypercholesterolaemia using alternative diagnostic and identification strategies. *Heart* 2011;**97**:1175–81.
19. Haralambos K, Ashfield-Watt P, Edwards R, Gingell R, Townsend D, et al. Five year experience of scoring criteria for familial hypercholesterolaemia (FH) genetic testing in Wales: Should the criteria be refined to include age? *Atherosclerosis* 2016;**255**:7–-8.
20. Mackie A, Humphries SE, Neil HAW, on behalf of the Simon Broome Register Committee. Screening for familial hypercholesterolaemia in adults in the UK and the UK NSC screening criteria. June 2011. Available at: https://legacyscreening.phe.org.uk/familialhypercholesterolaemia-adult. Accessed: January 2018.
21. Robson J, Dostal I, Sheikh A, Eldridge S, Madurasinghe V, et al. The NHS Health Check in England: an evaluation of the first 4 years. *BMJ Open* 2016;**6**:e008840..
22. Chang K, Millett C, Soljak M, Majeed A. National coverage of the English NHS Health Check programme. *Eur J Public Health* 2014;**24**:cku165-033.
23. Wald DS, Bestwick JP, Wald NJ. Child-parent screening for familial hypercholesterolaemia: Screening strategy based on a meta-analysis. *BMJ* 2007;**335**:599–603.
24. Wald DS, Bestwick JP, Morris JK, Whyte K, Jenkins L, et al. Child–Parent Familial Hypercholesterolemia Screening in Primary Care. *N Engl J Med* 2016;**375**:1628–37.
25. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. NICE, April 2013. Available at:

https://www.nice.org.uk/process/pmg9/chapter/the-reference-case. Accessed: January 2018.

26. Marks D, Wonderling D, Thorogood M, Lambert H, Humphries SE, et al. Screening for hypercholesterolaemia *versus* case finding for familial hypercholesterolaemia: a systematic review and cost effectiveness analysis. *Health Technol Assess* 2000; 4:1–123.
27. Fouchier SW, Hutten BA, Defesche JC. Current novel-gene-finding strategy for autosomal-dominant hypercholesterolaemia needs refinement. *J Med Genet* 2015;**52**:80–4.
28. Steering Group for the Department of Health Familial Hypercholesterolaemia Cascade Testing Audit Project. Family tracing to identify patients with Familial Hypercholesterolaemia: the second Audit of the Department of Health Familial Hypercholesterolaemia Cascade Testing Project. *Ann Clin Biochem* 2009;**46**:24–32.
29. Damgaard D, Larsen ML, Nissen PH, Jensen JM, Jensen HK, et al. The relationship of molecular genetic to clinical diagnosis of familial hypercholesterolemia in a Danish population. *Atherosclerosis* 2005;**180**:155–60.
30. Humphries SE, Cranston T, Allen M, Middleton-Price H, Fernandez MC, et al. Mutational analysis in UK patients with a clinical diagnosis of familial hypercholesterolaemia: relationship with plasma lipid traits, heart disease risk and utility in relative tracing. *J Mol Med* 2006;**84**:203–14.
31. Umans-Eckenhausen MA, Defesche JC, Sijbrands EJ, Scheerder RL, Kastelein JJ. Review of first five years of screening for familial hypercholesterolaemia in the Netherlands. *Lancet* 2001;**357**:165–8.
32. National Clinical Guideline Centre. NICE clinical guideline CG181: Lipid modification: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. Clinical Guideline Appendices. NICE, July 2014 (updated September 2016). Available at: https://www.nice.org.uk/guidance/cg181/evidence. Accessed: January 2018.
33. Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, Minhas R, et al. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. *BMJ* 2008;**336**:1475–82.
34. Bhatnagar P, Wickramasinghe K, Wilkins E, Townsend N. Trends in the epidemiology of cardiovascular disease in the UK. *Heart* 2016;**102**:1945–1952.
35. Office for National Statistics. Mortality statistics - underlying cause, sex and age [dataset]. Available at: https://www.nomisweb.co.uk/query/select/getdatasetbytheme.asp?opt=3&theme=&subgrp=. Accessed: September 2017.

1 36. Office for National Statistics. Population estimates - local authority based by five year
2 age band [dataset]. Available at:
3 https://www.nomisweb.co.uk/query/select/getdatasetbytheme.asp?theme=32
4 Accessed: September 2017.
5 37. Ramaswami U, Cooper J, Humphries SE. The UK Paediatric Familial
6 Hypercholesterolaemia Register: Preliminary data. *Arch Dis Child* 2017;**102**:255–60.
7 38. Cholesterol Treatment Trialists Collaboration. Efficacy and safety of more intensive
8 lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26
9 randomised trials. *Lancet* 2010 **376**:1670–81.
10 39. de Jongh S, Kerckhoffs MC, Grootenhuis MA, Bakker HD, Heymans HS, et al. Quality of
11 life, anxiety and concerns among statin-treated children with familial
12 hypercholesterolaemia and their parents. *Acta Pædiatr* 2003;**92**:1096–101.
13 40. Retterstøl K, Stugaard M, Gørbitz C, Ose L. Results of intensive long-term treatment of
14 familial hypercholesterolemia. *Am J Cardiol* 1996;**78**:1369–74.
15 41. Office for National Statistics. National life tables: England and Wales 2014-16 [dataset].
16 ONS, September 2017. Available at:
17 https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/li
18 feexpectancies/datasets/nationallifetablesenglandandwalesreferencetables. Accessed:
19 September 2017.
20 42. Morris JK, Wald DS, Wald NJ. The evaluation of cascade testing for familial
21 hypercholesterolemia. *Am J Med Genet A* 2012;**158a**:78–84.
22 43. Wald DS, Kasturiratne A, Godoy A, Ma L, Bestwick JP, et al. Child-Parent Screening for
23 Familial Hypercholesterolemia. *J Pediatr* 2011;**159**:865–67.
24 44. Marks D, Wonderling D, Thorogood M, Lambert H, Humphries SE, et al. Cost
25 effectiveness analysis of different approaches of screening for familial
26 hypercholesterolaemia. *BMJ* 2002;**324**:1303.
27 45. Ademi Z, Watts GF, Juniper A, Liew D. A systematic review of economic evaluations of
28 the detection and treatment of familial hypercholesterolemia. *Int J Cardiol*
29 2013;**167**:2391–6.
30 46. Futema M, Cooper JA, Charakida M, Boustred C, Sattar N, et al. Screening for familial
31 hypercholesterolaemia in childhood: Avon Longitudinal Study of Parents and
32 Children (ALSPAC). *Atherosclerosis* 2017;**260**:47–55.
33 47. Besseling J, Kastelein JP, Defesche JC, Hutten BA, Hovingh GK. Association between
34 familial hypercholesterolemia and prevalence of type 2 diabetes mellitus. *JAMA*
35 2015;**313**:1029–36.

48. Vuorio A, Strandberg TE, Schneider WJ, Kovanen PT. Statins and new-onset diabetes mellitus - a risk lacking in familial hypercholesterolaemia. *J Intern Med* 2016;**279**:358–61.

49. Besseling J, Sjouke B, Kastelein JJP. Screening and treatment of familial hypercholesterolemia - Lessons from the past and opportunities for the future (based on the Anitschkow Lecture 2014). *Atherosclerosis* 2015;**241**:597–606.

50. Kusters DM, de Beaufort C, Widhalm K, Guardamagna O, Bratina N, et al. Paediatric screening for hypercholesterolaemia in Europe. *Arch Dis Child* 2012;**97**:272-276.

51. Ritchie SK, Murphy EC, Ice C, Cottrell LA, Minor V, et al. Universal *versus* targeted blood cholesterol screening among youth: The CARDIAC project. *Pediatrics* 2010:**126**;260–265.

52. Williams RR, Hunt SC, Barlow GK, Chamberlain RM, Weinberg AD, et al. Health family trees: a tool for finding and helping young family members of coronary and cancer prone pedigrees in Texas and Utah. *Am J Public Health* 1988;**78**:1283-86.

53. National Heart, Lung and Blood Institute. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report. *Pediatrics* 2011;**128**:S213-S256.

54. Bazian Ltd for the UK National Screening Committee. Screening for familial hypercholesterolaemia in childhood: External review against programme appraisal criteria for the UK National Screening Committee (UK NSC). March 2015. Available at: https://legacyscreening.phe.org.uk/familialhypercholesterolaemia-child. Accessed: January 2018.

55. Tonstad S. Familial hypercholesterolaemia: a pilot study of parents'and children's concerns. *Acta Pædiatr* 1996;**85**:1307–13.

56. Andersen LK, Jensen HK, Juul S, Faergeman O. Patients' attitudes toward detection of heterozygous familial hypercholesterolemia. *Arch Intern Med* 1997;**157**:553–60.

57. Meulenkamp TM, Tibben A, Mollema ED, van Langen IM, Wiegman A, et al. Predictive genetic testing for cardiovascular diseases: Impact on carrier children. *Am J Med Genet A* 2008;**146A**:3136–46.

58. Sharifi M, Rakhit RD, Humphries SE, Nair D. Cardiovascular risk stratification in familial hypercholesterolaemia. *Heart* 2016;**102**:1003-1008.

Legends

Figure 1 – Decision tree and Markov model structures.

(A) Decision tree used to estimate universal screening outcomes for each alternative. Outcomes were modelled separately for the FH-positive and FH-negative individuals in each cohort, according to the probabilities and formulae described in Table 1 and Supplementary File 2, respectively. 'Reflex' testing (i.e. of samples already collected) applied where possible to minimize test requirements.

(B) Markov model health states and connections. N.B. 'Post-event' states accessible from associated event states only.

TC: total cholesterol; CVD: cardiovascular disease; MI: myocardial infarction; TIA: transient ischaemic attack; CHD: coronary heart disease

Table 1: Probabilities applied in calculation of decision tree outcomes.

Probability	Notation	Value	Calculation/rationale	References[c]
All scenarios				
FH-positive (undiagnosed)[a,b]	p(FH+)	0·0034	85% of estimated FH prevalence	Akioyamen et al., 2017, Nordestgaard et al., 2013, Pedersen et al., 2010
FH-negative[b]	p(FH-)	0·9966	1 – p(FH+)	
Mutation-positive given FH+	p(M+|FH+)	0·45	Probabilities reported from UK studies = 40.7% and 47.0%, within the range of values reported internationally (38.5-57.0%).	Futema et al., 2013, Graham et al., 2005, Damgaard et al., 2005, Klančar et al., 2015, Civeira et al., 2008
Mutation-negative given FH+	p(M-|FH+)	0·55	1 - p(M+|FH+)	
Mutation-positive	p(M+)	0·0019	(1/250)*p(M+|FH+)/0·95	
Mutation-positive given FH-	p(M+|FH-)	$9{\cdot}51*10^{-5}$	p(M+) – (1/250)*p(M+|FH+)/p(FH-) (based on meta-analysis results indicative that ≥95% of M+ infants exhibit hypercholesterolaemia.	Wald et al., 2007, 2016
Mutation-negative given FH-	p(M-|FH-)	$1 - 9{\cdot}51*10^{-5}$	1 – p(M+|FH-)	
First appointment attendance	p(A1)	0·92	2015-16 UK 24-month vaccination coverage	NHS Immunisation Statistics
First test participation	p(P1)	0·94	As per recent UK US study	Wald et al., 2016
Second appointment attendance	p(A2)	0·92	2015-16 UK 24-month vaccination coverage	NHS Immunisation Statistics
Second test participation	p(P2)	0·94	Willingness to participate in further screening reported in UK US study	Wald et al., 2016
Second elevated TC test following elevated first test	p(TC2+|TC1+)	0·935	Pre-diagnosis duplication of elevated measurement recommended, in view of biological and analytical test variability	Nordestgaard et al., 2013, Watts et al., 2015, NICE CG71, Neil, 1996
Cholesterol-only screening scenario				
Positive TC tests given FH+	p(TC+|FH+)	0·88	This threshold applied as post-test probability (=0.78) reasonably low (and 0.43 at next lowest threshold for which test performance figures described)	Wald et al., 2007
Positive TC tests given FH-	p(TC+|FH-)	0·001		
Sequential genetic-TC and parallel TC-genetic screening scenarios				
Positive TC tests given FH+	p(TC+|FH+)	1	By definition	
Positive TC tests given FH-	p(TC+|FH-)	0	By definition	
Negative TC tests among FH-	p(TC-|FH-)	1	By definition	
Sequential TC-genetic screening scenario				
Positive TC tests among FH+	p(TC+|FH+)	0·96	Lowest threshold for which test performance described. Found by UK US study to be above general population 95th percentile.	Wald et al., 2007, 2016
Positive TC tests among FH-[a]	p(TC+|FH-)	0·045	0·05 – (1/250)	

[a]1/250 = estimated FH prevalence; 0·95 = estimated proportion of those mutation-positive with total cholesterol ≥95th percentile (Wald et al, 2007, 2016); [a,b]Estimated prevalence figures recalculated for threshold analyses; [c]full references in Supplementary File 9.

FH: familial hypercholesterolaemia; TC: total cholesterol; US: universal screening.

Table 2: Base case screening, treatment and health state costs

	Cost/item (as listed)	Details and references[d]
Screening		
Nursing time:		
- first US appointment	£17.07	On local clinical expert advice, 30 min allocated for first US appointment, 15 min for second; 45 min for RCT consultation with index case, 30 min for consultation with relatives. Time costed for band 7 nurse specialist [a]
- second US appointment	£8.54	
- index case consultation for CT	£25.61	
- initial relative CT appointment	£17.07	
NGS screen	£263	2017-18 local laboratory NHS costs (Bristol Genetics Laboratory, 2017)
Genetic test for known mutation	£79	
Lipid profile test	£3	2014 CG181 GDG estimate (in keeping with recently published values)
Results/appointment invitation letter	£1.09	CPI-uplifted 2009 NICE FH costing template values
Administrator time per letter	£4.92	Time costed for band 5 administrator [a]
Initial specialist review (paediatric)	£316.70	2017-18 National Tariff first endocrinology outpatient review*mean MFF (NHS England)
Initial specialist review (adult)	£239.96	
Treatment		
Average annual LMT (8-9 years)	£10.31	September 2017 Drug Tariff (NHS Business Services Authority)
Average annual LMT (10-17 years)	£17.14	
Average annual LMT (adult)	£204.11	
Lipid profile test	£3	2014 NICE CG181 GDG estimates (in keeping with recently published values)
Liver function tests	£1	
Creatine kinase test	£2	
Blood sampling appointment (paediatric)	£5.01	20 min (paediatric) or 15 min (adult) of band 3 phlebotomist time [a]
Blood sampling appointment (adult)	£3.76	
Secondary care follow-up (paediatric)	£156.73	2017-18 National Tariff follow-up endocrinology outpatient review*mean MFF (NHS England)
Secondary care follow-up (adult)	£100.52	
Primary care follow-up (adult)	£37.00	2017 face-to-face GP consultation cost (PSSRU)
Health state costs (annual)		
Well and dead states	£0	CPI-adjusted CG181 estimates [b c]
Stable angina	£8280	
Post-stable angina	£252.95	
Unstable angina	£3694.70	
Post-unstable angina	£405.78	
Myocardial infarction	£3932.37	
Post-myocardial infarction	£830.53	
Transient ischaemic attack	£674.54	
Post-transient ischaemic attack	£130.69	
Stroke	£4394.53	
Post-stroke	£163.37	

[a]Staff time costed using 2017-18 band midpoint salaries plus oncosts, assuming full-time working with 80% (nursing, phlebotomy) and 90% (administration) clinical time (NHS Staff Council, 2017; HMRC, 2017; NHS Business Services Authority, 2017); [b]originally calculated based on guideline-recommended management; interim updates have been few, the main update being extension of stroke thrombolysis window from 3 to 4·5

hours (NICE CG68); [c]CPI used rather than health care specific index as figures available to more recent dates and higher overall, providing more conservative estimate; [d]full references in Supplementary File 9.

US: universal screening; (R)CT: (reverse) cascade testing; NGS: next generation sequencing; LMT: lipid modification therapy; GDG: guideline development group; CPI: consumer price index; FH: familial hypercholesterolaemia; NICE: National Institute for Health and Care Excellence; MFF: market forces factor; GP: general practitioner; PSSRU: Personal Social Services Research Unit.

Table 3: Summary of deterministic sensitivity analyses

DSA-specific adjustment	Rationale	References[d]
All M+ defined as FH+	Both extent and duration of raised LDL-C influence CVD risk; hence M+ status associated with relatively high risk for given current LDL-C	Khera et al., 2016, Damgaard et al., 2005
RCT case yield/index = 0·5	Reflective of current CT achievement	Hadfield et al., 2009, Kerr et al., 2017, Marks, 2006
RCT case yield/index = 6·1	Theoretical maximum achievable under current UK approach to CT.	Morris et al., 2012
RCT case yield/index = 8·6; probability relative M+ = 0·21	Achieved in The Netherlands; theoretical maximum achievable in UK If first- to third- degree relatives screened unconditionally. Cases (n=2·5) identified with probability of second- versus third- degree relatives unclear, therefore analysed assuming all second-degree, repeated assuming all third-degree.	Umans-Eckenhausen, 2001, Morris et al., 2012
RCT case yield/index = 8·6; probability relative M+ = 0·31		
100% of diagnosed adults treated		
100% of diagnosed treated from 8 years		
15% discontinue LMT at 10 years	Potential LMT discontinuation/reduced adherence (reportedly, 84%+ treated, with ≥80% regime-adherent, at 10 years, but rates may fall over time)[a]	Kusters et al., 2014, Galema-Boers et al., 2014
50% LDL-C reduction achieved with LMT	NICE CG71 recommendation	
Estimated off-patent LMT costs applied	Patents protecting rosuvastatin and ezetimibe due to expire this year[b]	September 2017 Drug Tariff, NHS Business Services Authority, Kerr et al., 2017
Discount rate = 1·5%		
Discount rate = 5·0%		
CVD risks 90% of base case estimates	It has not been possible to obtain unbiased estimates of untreated secondary event risks since LMT introduction. General population CVD risk has fallen in the meantime, and a continuing downward trajectory is predicted.	Bhatnagar et al., 2016
CVD risks 80% of base case estimates		
Undiagnosed cases treated at background rate	Treatment prior to diagnosis plausible[c]	Nanchen et al., 2015, Carey et al., 2012, O'Keeffe et al., 2016, Fleetcroft et al., 2014
Cholesterol test sensitivity in sequential cholesterol-genetic US strategy = 62·5%	Recent finding detection rates with LDL-C threshold at approx. general population 95th percentile could be as low as 62·5% (lower using TC) (NB. n=6 mutation-positive children identified in study)	Futema et al., 2017
Time for first US appointment 40 min	Expert clinician suggestion	

[a]It was assumed that transition probabilities reverted to untreated values immediately on treatment discontinuation – likely conservative in view of treatment legacy effects.(Ford et al., 2016); [b]current costs of simvastatin regimes with equivalent LDL-C-reducing potency used to estimate off-patent rosuvastatin costs. Off-patent ezetimibe cost estimated using value recently predicted by Kerr et al. (10% of current cost); [c]80% of secondary prevention patients, and 20, 30, 40 and 50% of those that reached 40, 50, 60 and 70 years,

respectively, were treated (regardless of diagnosed/undiagnosed status); [d] full references in Supplementary File 9.

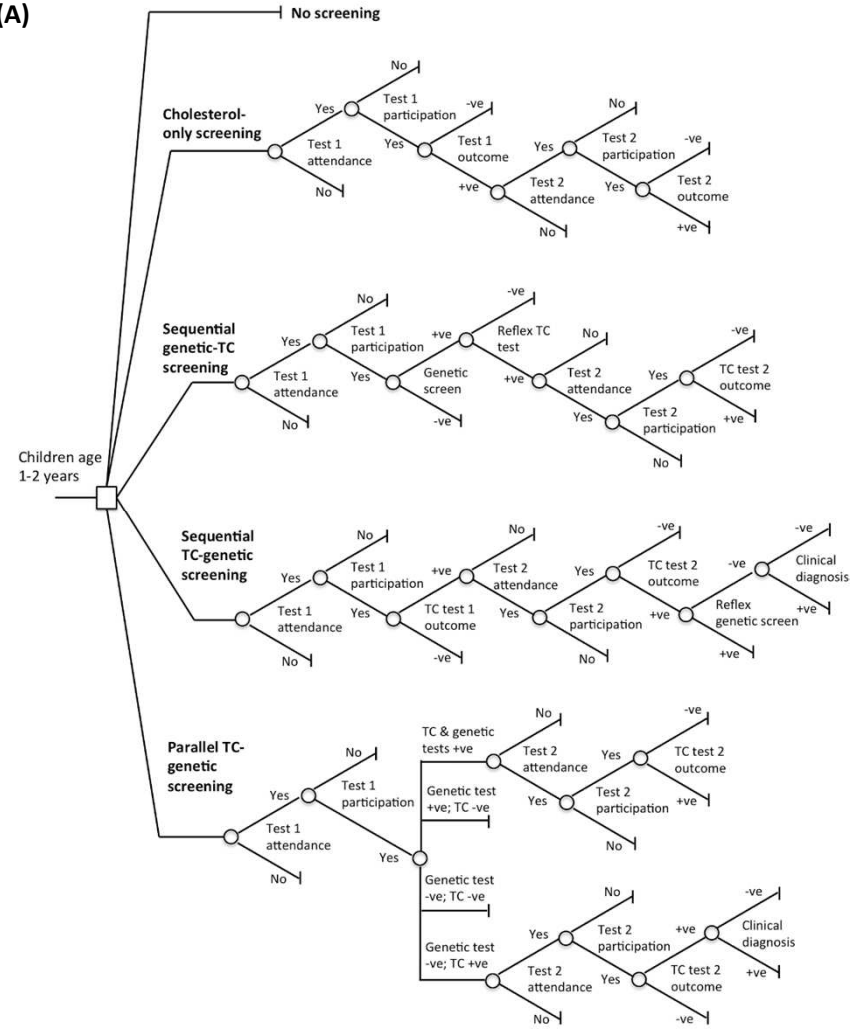
DSA: deterministic sensitivity analysis; M+: mutation-positive; (R)CT: (reverse) cascade testing; LMT: lipid modifying therapy; LDL-C: low density lipoprotein cholesterol; CVD: cardiovascular disease; US: universal screening; NICE: National Institute for Health and Care Excellence; TC: total cholesterol

Table 4: Case yields, costs per diagnosis and cost-effectiveness of screening alternatives

	FH cases identified per 10,000 screened			Screening costs per diagnosis (£)					ICER (£/QALY)		
	US	RCT	total	US	RCT	total	QALYs	Costs (£)	*versus* no screening	*versus* next lowest cost	*versus* relevant alternative
No screening	0	0	0	n/a	n/a	n/a	992·2	225,983	-	-	-
Cholesterol-only screening	22·38	0	22·38	11,788	n/a	11,788	1,009·1	561,071	19,298	19,298	ED
Sequential cholesterol-genetic screening	24·41	0	24·41	13,785	n/a	13,785	1,010·7	640,288	21,872	50,184	ED
Sequential cholesterol-genetic screening plus RCT	24·41	15·38	39·79	13,785	1,110	8,886	1,027·5	672,362	12,480	1,906	12,480
Sequential genetic-cholesterol screening	11·44	0	11·44	217,036	n/a	217,036	1,000·7	2,745,892	283,799	SD	SD
Sequential genetic-cholesterol screening plus RCT	11·44	19·67	31·11	217,036	1,110	80,519	1,022·2	2,786,918	84,240	SD	SD
Parallel cholesterol-genetic screening	25·43	0	25·43	98,959	n/a	98,959	1,011·5	2,823,343	131,635	SD	SD
Parallel cholesterol-genetic screening plus RCT	25·43	19·67	45·10	98,959	1,110	56,279	1,033·0	2,864,370	63,957	399,581	399,581

FH: familial hypercholesterolaemia; US: universal screening; RCT: reverse cascade testing; QALY: quality adjusted life year; ICER: incremental cost-effectiveness ratio; RCS: reverse cascade screening; ED: extendedly dominated; SD: strongly dominated

(A)



(B)

Entry state	Well (no existing CVD)
Potential first transition states	Stable angina; Unstable angina; MI; TIA; Stroke
Potential second transition states	Post-stable angina; Post-unstable angina; Post-MI; Post-TIA; Post-stroke; Unstable angina; MI; Stroke
Potential third (and subsequent) transition states	Post-unstable angina; Post-MI; Post-stroke; Unstable angina; MI; Stroke
Dead states accessible from any other state	CHD death; Non- CHD CVD death; Non-CVD death