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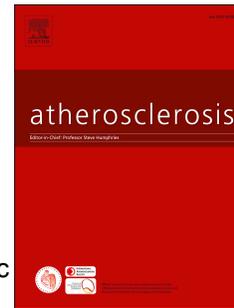
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Universal screening at age 1–2 years as an adjunct to cascade testing for familial hypercholesterolaemia in the UK: A cost-utility analysis

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

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22

1 Abstract

2

3 *Background and aims:* Familial hypercholesterolaemia (FH) is widely underdiagnosed.
4 Cascade testing (CT) of relatives has been shown to be feasible, acceptable and cost-effective
5 in the UK, but requires a supply of index cases. Feasibility of universal screening (US) at age
6 1-2 years was recently demonstrated. We examined whether this would be a cost-effective
7 adjunct to CT in the UK, given the current and plausible future undiagnosed FH prevalence.

8

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

18

19 *Results:* A strategy involving cholesterol screening followed by diagnostic genetic testing and
20 RCT was the most cost-effective modelled (incremental cost-effectiveness ratio (ICER)
21 *versus* no US £12,480/quality adjusted life year (QALY); probability of cost-effectiveness
22 96.8% at £20,000/QALY threshold). Cost-effectiveness was robust to both deterministic
23 sensitivity analyses and threshold analyses that modelled ongoing case ascertainment at
24 theoretical maximum levels.

25

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

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

1 Introduction

2 Familial hypercholesterolaemia (FH) is characterised by elevated low-density lipoprotein
3 cholesterol (LDL-C) from birth, and is associated with elevated risk of coronary heart disease
4 (CHD).¹ A recent general population study described an odds of CHD for the average
5 untreated FH phenotype around 13-fold higher than that of the non-FH phenotype.² This
6 relative risk is age-dependent, being higher in younger age-groups.³ Mortality at <30 years is
7 typical of untreated homozygous disease,⁴ whereas the heterozygous genotype confers
8 approximately 50% risk of CHD by 50 years among males, and 30% risk of CHD by 60 years
9 in females.^{5 6} Recent prevalence estimates for heterozygous disease range from 1/250-1/200
10 (1/300,000-1/160,000 for homozygous disease).^{7 8} It is therefore anticipated that there are
11 approximately 187,500-328,200 people with FH in the UK, but estimates suggest fewer than
12 15% have been diagnosed.^{9 10} Those undiagnosed represent a substantial reservoir of
13 potentially modifiable cardiovascular disease (CVD) risk.

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

26
27 Since 2008, the UK National Institute for Health and Care Excellence (NICE) has
28 recommended cascade testing (CT, of first-, second- and third- degree relatives) for FH,¹⁶
29 and this has been shown to be feasible, acceptable and cost-effective.^{17 18} There has been
30 limited roll-out of CT in England, as local teams have not commissioned the relevant
31 services, but it has been relatively successful in other parts of the UK.¹⁹ As CT depends on
32 index case supply, there is interest in screening to identify index cases. Both adult and
33 childhood systematic population screening (or 'universal screening'; US) for FH remain
34 under review by the UK National Screening Committee (NSC). Recent NSC external review
35 has considered that the NHS Health Check may represent an adulthood FH screening
36 mechanism,²⁰ but we are unaware of data supporting this. Moreover, the reach of Health
37 Checks is restricted and increasingly so under the current contraction of UK local public

1 health budgets.^{21 22} Feasibility of otherwise screening in adulthood has not been demonstrated,
2 and no model for adult screening has been described. There are also theoretical reasons to
3 favour screening in childhood. The false positive and false negative FH case detection rates
4 for given cholesterol thresholds appear to be most favourable at young ages,²³ and screening
5 at younger ages enables intervention at an early stage of atherosclerosis development, when
6 maximum benefit can still be obtained via lifestyle adaptations and LMT. The feasibility of
7 US at age 1-2 years has recently been demonstrated,²⁴ but cost-effectiveness is unclear.

8
9 We therefore aimed to determine whether US for FH at 1-2 years could be a cost-effective
10 adjunct to CT in the UK. Our main objective was to compare the cost-effectiveness of
11 cholesterol and/or mutation-based US \pm reverse cascade testing (RCT; where feasible)
12 alternatives (detailed in Box 1), at current undiagnosed FH prevalence. We also examined
13 whether there would be a point at which US would lose cost-effectiveness (due to falling FH
14 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

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1 **Materials and methods**

2

3 **Comparators, approach and perspective**

4 The alternatives described in Box 1 were compared (with reference to heterozygous FH only)
5 from a UK NHS healthcare perspective. Methods were aligned with the NICE reference case
6 so far as possible,²⁵ in an incremental analysis that estimated lifetime (to a maximum of 100
7 years) costs and health outcomes (discounted at 3.5% per annum) for cohorts screened under
8 each alternative. Where possible, modelling was based on UK data, and UK diagnostic
9 criteria and treatment pathways. In the base case, definition of FH (for treatment purposes)
10 was therefore a Simon Broome diagnosis *plus* hypercholesterolaemia (defined as total
11 cholesterol exceeding the general population 95th percentile).^{26 27} All (and only) mutation-
12 positive individuals were considered as index individuals for RCT.

13

14 The model had three main components:

15

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

22

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

28

29 **Model structure and inputs**

30 The decision tree used to model US (Figure 1a) reflects simplified versions of the screening
31 pathway used in the recent UK study that demonstrated US feasibility.²⁴ The associated
32 probabilities (Table 1) were combined to derive outcomes for each screening cohort
33 (Supplementary File 2). We assumed there was no delay between US case-identification and
34 RCT, and based on local data and an expectation that a US programme would facilitate
35 improved CT,^{24 28} estimated base case RCT yield was two mutation-positive individuals per
36 mutation-positive index individual. That is, where RCT was part of the screening alternative

1 it was assumed two mutation-positive individuals would be identified via RCT for every
2 mutation-positive individual identified in US. It was assumed the age-distribution of those
3 identified by RCT would be as observed in the Welsh CT programme,¹⁷ and that 70% of
4 RCT-identified mutation-positive relatives would meet the base case FH definition.²⁹⁻³¹ For
5 purposes of costing RCT (see below), probability of mutation detection among relatives was
6 assumed to be Mendelian.

7
8 Separate Markov models estimated outcomes for cohorts of 1,000 diagnosed or undiagnosed
9 individuals, starting from age two years, five years, and each subsequent five-year interval to
10 85 years. The modelling approach followed that used in the economic evaluation for NICE
11 CG181, and a recent CT analysis, and is described fully in Supplementary File 3.^{17 32} Briefly,
12 baseline CVD risks drew on the QRISK2 model,³³ and the modelled health states included all
13 constituent diagnoses of the QRISK outcome (see Figure 1b). Where QRISK2 was not
14 validated for age-groups of interest, CVD risks were estimated using age-related CVD
15 relative risks calculated from published data.³⁴ The relative CHD death risks described for the
16 pre-treatment era Simon Broome cohort were applied to the angina, MI and CHD death risks.³
17 Individuals progressed to post-CVD states in the cycle following development of non-fatal
18 CVD, unless a further event or death occurred immediately. Secondary event risks obtained
19 from NICE CG181 (with some adjustments – see Supplementary File 3) were applied without
20 adjustment for FH,³² but the models did not allow for impact of multiple previous events.
21 Non-CVD mortality was estimated from 2015 England and Wales Office for National
22 Statistics mortality and mid-year population figures,^{35 36} and it was assumed that CVD and
23 mortality risks for the youngest age-group (not specifically reported), were zero. Modelled
24 treatment was based on national guidance and local audit and registry data, and was modelled
25 until age 60 years (details in Supplementary File 4).^{10 16 37} Welsh FH audit age-band-specific
26 pre-treatment LDL-C levels (concordant with national paediatric register data) were applied,¹⁷
27 and 37% treatment-related LDL-C reduction modelled in the base case (as observed in the
28 UK 2010 national FH audit,¹⁰ cf. 35% in paediatric register).³⁷ Resultant expected treatment-
29 related absolute LDL-C reductions were transformed to CVD relative risk reductions using
30 the Cholesterol Treatment Trialists' (CTT) Collaboration-reported per mM values for non-
31 fatal MI, ischaemic stroke, and CHD death (applied to angina and MI, TIA and stroke, and
32 CHD death, risks, respectively).³⁸ The CTT values were assumed applicable to both primary
33 and secondary events.

34
35 Cycle health state outcomes were weighted with the utilities described in CG181,³² and costs
36 and effects were discounted, enabling calculation of discounted quality-adjusted life year
37 (QALY) and cost outcomes for each model. Models assumed no FH- or LMT- associated

1 disutility, as per previous observation,^{39 40} and assumption that treatment-related disutility
2 would prompt treatment modification, averting its persistence. To determine overall Markov
3 model outcomes for each alternative, the outcomes from each model were combined
4 according to the age-distribution and diagnosed/undiagnosed status of the individuals
5 identified by US and RCT in at least one of the screening scenarios, for each alternative.
6

7 **Resource use and costs**

8 Costs were calculated in 2017 GBP. Modelled costs were current where possible, otherwise
9 inflated to 2017 values, and assumed to remain constant (subject to discounting) over the
10 model duration. Table 2 summarises the costs applied. Total US costs were estimated for
11 each cohort by multiplying individual costs*probability of being incurred under the relevant
12 strategy*10,000. CT costs per index individual were estimated as the costs of index individual
13 consultation, plus screening costs for identified relatives (based on CG71 CT
14 recommendations and associated costing template)*the inverse of the probability of a relative
15 being affected. Patient monitoring costs were applied only when patients were receiving
16 LMT, except in cases of LMT-naïve individuals <18 years. At all ages, annual monitoring
17 included blood sampling, lipid profile testing, and medical review (secondary care review at
18 <18 years; 80:20 secondary:primary care split at ≥18 years).^{10 28} Creatine kinase and 2x liver
19 function tests were costed for the first treatment year, plus an additional secondary care
20 review if this was not the screening year.
21

22 **Management of uncertainty and calculations**

23 To include parameter uncertainty, Markov models were built probabilistically, with beta
24 distributions applied for transition probabilities and utilities, log-normal distributions for the
25 CVD relative risks associated with FH and LDL-C reduction, and normal distribution for the
26 pre-treatment LDL-C estimates (details in Supplementary File 5). 1,000 Monte Carlo
27 simulations were run for each model. Uncertainty was further explored in a series of one-way
28 DSAs, as outlined in Table 3, and the impact of including treatment costs for false positives
29 identified in the cholesterol-only screening alternative (assuming treatment as per true
30 positives, with estimated survival based on current standard life tables),⁴¹ was also
31 considered.
32

33 In all analyses, ICERs were calculated for each alternative *versus* the next lowest cost.
34 Dominated comparators were excluded and the remaining alternatives compared to the
35 remaining next lowest cost, repeated as necessary. Cost-effectiveness was assessed using the
36 £20,000-£30,000 NICE willingness-to-pay threshold,²⁵ and cost-effectiveness acceptability
37 curves were plotted. Threshold analysis estimated the undiagnosed FH prevalences at which

1 the ICER for the most cost-effective screening strategy crossed £20,000/QALY and
2 £30,000/QALY willingness-to-pay thresholds, under otherwise base case conditions \pm off-
3 patent LMT costs (see Table 3). Scenarios in which CT yields were 2.4, 6.1 and 8.6
4 cases/index, and undiagnosed FH prevalences were 67, 33 and 24%, respectively, were also
5 considered, as theoretical analyses indicate that such undiagnosed prevalences could not be
6 reached with these CT yields.⁴² Analyses were carried out using MS Excel v14.7.7.

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1 Results

2 The sequential cholesterol screening-genetic testing plus RCT strategy was the most cost-
3 effective in all analyses, and no scenario identified an additional strategy that could be cost-
4 effectively provided. The number of FH cases identified under each screening strategy, costs
5 per diagnosis, average QALYs gained, overall costs, and associated ICERs, are displayed in
6 Table 4 (DSA estimates in Supplementary Files 6 and 7). Diagnosis rates ranged from
7 11.4/10,000 screened (sequential genetic testing-cholesterol screening) to 25.4/10,000
8 (parallel cholesterol screening-genetic testing) without RCT, and 31.1/10,000 to 45.1/10,000
9 (same US strategies) with RCT. Costs per US diagnosis ranged from £11,788 (cholesterol-
10 only screening) to £217,036 (sequential genetic-cholesterol screening). Cost per RCT
11 diagnosis was £1,110. The lowest overall cost per diagnosis (£8,886) was observed for the
12 sequential cholesterol screening-genetic testing plus RCT strategy, which also achieved the
13 second highest number of diagnoses (39.8/10,000). The ICER for this strategy *versus* no
14 screening (£12,480/QALY) dominated all others except the parallel cholesterol-genetic US
15 plus RCT scenario (ICER for direct comparison =£399,581/QALY).

16
17 As expected, ICERs were sensitive to RCT success, ranging from £6,269-£6,729/QALY to
18 £18,253/QALY across the RCT yields tested. Discounting at 1.5%, and 50% treatment-
19 related LDL-C reduction, were associated with relatively low ICERs (£5,489/QALY and
20 £7,733/QALY, respectively). Only discounting at 5% produced an ICER >£20,000/QALY
21 (£20,849/QALY). Cost-effectiveness acceptability curves for the sequential cholesterol
22 screening-genetic testing US plus RCT *versus* no screening comparison are displayed for
23 several scenarios in Supplementary File 8. For the base case, probability of cost-effectiveness
24 was 96.8% at a willingness-to-pay threshold of £20,000/QALY (100% at £30,000/QALY).

25
26 Threshold analysis suggested US would be cost-effective at a £20,000/QALY threshold until
27 undiagnosed prevalence reached <48% (<30% for £30,000/QALY threshold). Corresponding
28 prevalences were <43% and <28% with off-patent LMT costs. ICERs for the scenarios in
29 which undiagnosed prevalences of 67%, 33% and 24%, and respective CT yields of 2.4, 6.1
30 and 8.6 cases per index, were modelled, were £13,692/QALY, £14,630/QALY and £15,680-
31 £16,146/QALY, respectively (£11,745/QALY, £12,851/QALY and £13,653-14,115/QALY
32 with off-patent LMT costs).

33

34

1 **Discussion**

2 **Summary of findings**

3 This study aimed to assess which of seven potential FH US strategies would be most cost-
4 effective for the UK context, whether any would be cost-effective as per conventional NICE
5 definition, and whether US could reduce undiagnosed FH prevalence to levels at which it
6 would lose cost-effectiveness. Sequential cholesterol screening-genetic testing plus RCT was
7 the most cost-effective alternative modelled, and cost-effectiveness was robust to DSAs and
8 to reductions in undiagnosed prevalence that US could theoretically achieve.⁴² The modelled
9 approach - with screening incorporated into routine child healthcare appointments - is
10 efficient in terms of minimising user inconvenience, limiting additional healthcare costs, and
11 potentially promoting screening engagement. As cholesterol results can be obtained by a
12 point-of-care testing method, individuals with cholesterol levels below the threshold that
13 would trigger genetic testing could be immediately reassured. While a mutation is only
14 detected in a proportion of those with LDL-C above the threshold, a mutation confirms the
15 diagnosis for these individuals, and unequivocal DNA-based diagnostic testing of relatives
16 (so-called reverse cascade testing) can be undertaken. The clinical value of the approach is
17 achieved by provision of LMT at a relatively young age, before high LDL-C burden has
18 resulted in premature atherosclerosis and a CHD event.

19 20 **Comparison with existing literature**

21 Among 10,000 children eligible for US, the sequential cholesterol screening-genetic testing
22 plus RCT strategy we found to be most cost-effective identified fewer children with
23 hypercholesterolaemia plus an FH mutation (n=10.98) than reported per 10,095 children from
24 the recent US feasibility study (n=21 such cases identified).²⁴ This may be explained by the
25 fact that we accounted for non-attendance and non-participation, required
26 hypercholesterolaemia on two rather than one tests (i.e. accounted for biological and
27 analytical cholesterol variability), and used a slightly more restrictive definition of
28 hypercholesterolaemia. Chance may also be relevant as the numbers are small. Reported costs
29 per diagnosis were lower (\$2,900 and £3,500) in recent studies than in our study, but this
30 discrepancy is expected as in addition to the test costs ± limited consultation time they
31 considered, we allowed for more screening consultation time (as recommended by local
32 clinicians familiar with FH testing), administrative costs, and initial specialist review.^{24,43} We
33 did not find further recent estimates of diagnosis costs or US cost-effectiveness in children,
34 but a 2002 HTA estimated both for US at 16 years.²⁶ Comparability is limited by inflation and
35 methodological differences. Nonetheless, reported costs per diagnosis from the 2002 study
36 were £9,754 where clinically confirmed and £72,140 with genetic confirmation,²⁶ and the
37 corresponding costs per life year gained, (with discounting at 3%), £7,244 and £33,882.⁴⁴

1 Given the interim reductions in genetic screening costs, these values probably support that
2 those reported here are feasible.

3

4 The ICER of £12,480/QALY for sequential cholesterol screening-genetic testing plus RCT is
5 as expected higher than that recently estimated for CT from known cases (ICER =
6 £5,806/QALY).^{17 18} Although several parameters were modelled similarly in both analyses,
7 the CT analysis did not model identification of index cases,^{17 18} which depends on testing with
8 a much lower pre-test probability of disease, and is therefore associated with higher screening
9 costs per diagnosis. As US enables FH diagnosis at a relatively young age, the differential
10 latencies to treatment and impact on the natural history of the disease will also contribute to
11 the CT *versus* US cost-effectiveness differences.

12

13 **Strengths and limitations**

14 This study appears to be the first to consider the cost-effectiveness of universal screening for
15 FH at 1-2 years. The study compared the multiple screening options previously noted of
16 interest,⁴⁵ and recent local data were available to estimate several parameters.

17

18 The persistent uncertainty around the sensitivity and specificity of different cholesterol
19 thresholds,⁴⁶ although considered in DSA (where we modelled the proportion of those with
20 FH with cholesterol levels exceeding the threshold for genetic testing down to 62.5%), is an
21 important limitation of all work in this area, and sensitive to the definition of FH applied.
22 Additional limitations in parameter estimation included the required extrapolation of
23 treatment efficacy data from non-FH populations, beyond the duration of LMT trials, and
24 beyond the intermediate outcomes of paediatric trials, as well as extrapolation of the CTT
25 relative risk reduction estimates beyond primary events. Secondary CVD event risk estimates
26 were limited by the time lapsed since their description and lack of adjustment for FH. FH-
27 specific utility data are few, and those applied (from non-FH populations) were drawn from
28 studies that utilised a range of choice-based preference elicitation methods and samples
29 (including non-UK-based samples). As practical and ethical issues impact ability to
30 overcome some of these limitations, assumptions are necessary if a decision is to be made on
31 the basis of all information that *is* available. Although the assumptions will impact on
32 accuracy, several are common to previous models used in UK healthcare decision-making
33 (e.g. the HTA for lipid modification in prevention of CVD, and the HTA that led to
34 introduction of cluster testing for FH). The assumptions applied may therefore be reasonable
35 to UK healthcare decision-makers, and accuracy is potentially less of a concern if
36 conservative assumptions lead to outcomes below a fixed willingness-to-pay threshold, as in
37 this case.

1
2 The model structure necessarily followed a simplified version of treatment pathways and did
3 not include additional potential inputs such as dietetics and management of statin-attributable
4 diabetes, which appears in any case to be low in FH patients.^{47 48} The models also assumed no
5 pre-existing CVD, which will not always be the case.⁴⁹ Additional methodological limitations
6 included the one-way modelling of uncertainties in DSA, when some could theoretically be
7 realised in combination, and the ‘memoryless’ characteristic of Markov models which
8 constrained modelling of accumulating CVD burden. Regarding generalisability, economic
9 evaluations require analyses to be contextualised, and the study is therefore of most direct
10 relevance to the UK. However, as cost-effectiveness of US has not previously been
11 demonstrated for any setting, and cost-effectiveness in the UK is likely to be associated with
12 cost-effectiveness elsewhere, the findings are likely to be of wider relevance, and may prompt
13 review of the issue and analyses for non-UK contexts. Under-diagnosis is a global concern,
14 and universal screening is currently implemented, recommended and/or under consideration
15 by relevant bodies in various jurisdictions.⁵⁰⁻⁵³

16 17 **Implications for research and practice**

18 2016 UK NSC review recommended against US for FH. Lack of demonstrated cost-
19 effectiveness was a concern, but also practical feasibility, acceptability, and lack of evidence
20 that US would reduce morbidity and mortality.⁵⁴ Feasibility of direct demonstration of impact
21 on morbidity and mortality has been questioned, as the ethical and time demands of clinical
22 endpoint trials are likely unachievable. However, the feasibility of US has now been
23 demonstrated, in a study that also indicated acceptability among parents,²⁴ and other studies
24 have similarly found that participants generally consider such screening beneficial.^{39 55-57}
25 Together with our findings, which would conventionally (i.e. under the standard NICE
26 threshold) support implementation of US, these studies support reconsideration of US.
27 Cholesterol thresholds of alternative sensitivity/specificity (which may impact on US
28 acceptability) could be considered in future analyses, when test performance at these
29 thresholds has been described.

30
31 Our analyses focused on screening at age 1-2 years, in view of recently demonstrated
32 feasibility for this age-group. Whilst this may be considered an appropriate age for screening
33 in some contexts, others have shown interest in screening school-age children.⁵⁰⁻⁵³ The
34 economic implications of screening at slightly higher ages are likely to be minimal, and
35 screening at such ages could again be linked to other routine childhood healthcare
36 attendances. Vaccination uptake rates indicate that this would be unlikely to have a major
37 impact on screening participation, at least in the UK. A key issue for decisions about optimal

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

9 **Conclusions**

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

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1 Conflict of interest

2 AJM, HH, DM and AM report no competing interests. SEH is the Medical Director and
3 minority shareholder of a UCL spin-out company called StoreGene, which uses a 20 SNP
4 genetic test, in combination with the classical risk factor profile, for estimating an
5 individual's future risk of CVD, and which offers genetic testing for FH through an
6 accredited diagnostic laboratory. SEH is a consultant for Color Genomics which offers
7 genetic tests for FH in the US, and reports grants from the British Heart Foundation and
8 International Atherosclerosis Society-Pfizer, outside the submitted work. SEH was one of the
9 topic experts for the 2017 NICE FH guideline update of the 2008 FH guideline CG71. KKR
10 reports grants from Sanofi, Regeneron, Amgen, Pfizer and MSD, outside the submitted work.
11 KKR reports personal fees from Sanofi, Amgen, Regeneron, Pfizer, Kowa, Algorithm,
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14

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17 the NIHR UCLH BRC.

18

19 Author contributions

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

22

23 Ethics statement

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

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1 **References**

- 2 1. Brown MS, Goldstein JL. A receptor-mediated pathway for cholesterol homeostasis.
3 *Science* 1986;**232**:34–47.
- 4 2. Benn M, Watts GF, Tybjaerg-Hansen A, Nordestgaard BG. Familial Hypercholesterolemia
5 in the Danish General Population: Prevalence, Coronary Artery Disease, and
6 Cholesterol-Lowering Medication. *Journal Clin Endocrinol Metab* 2012;**97**:3956–64.
- 7 3. Scientific Steering Committee on behalf of the Simon Broome Register Group. Risk of
8 fatal coronary heart disease in familial hypercholesterolaemia. *BMJ* 1991;**303**:893–
9 96.
- 10 4. Goldstein JL, Hobbs HH, Brown MS, Scriver CR, Beaudet AL, et al. Familial
11 hypercholesterolemia. The metabolic and molecular bases of inherited disease, 8th
12 ed. New York: McGraw-Hill, 2001. (pp. 2863-2913).
- 13 5. Slack J. Risks of ischaemic heart disease in familial hyperlipoproteinaemic states. *Lancet*
14 1969;**294**:1380–82.
- 15 6. Stone NJ, Levy RI, Fredrickson DS, Verter J. Coronary Artery Disease in 116 Kindred with
16 Familial Type II Hyperlipoproteinemia. *Circulation* 1974;**49**:476–88.
- 17 7. Akioyamen LE, Genest J, Shan SD, Reel RL, Albaum JM, et al. Estimating the prevalence
18 of heterozygous familial hypercholesterolaemia: a systematic review and meta-
19 analysis. *BMJ Open* 2017;**7**:e016461.
- 20 8. International Atherosclerosis Society Severe Familial Hypercholesterolaemia Panel.
21 Defining severe familial hypercholesterolaemia and the implications for clinical
22 management: a consensus statement from the International Atherosclerosis Society
23 Severe Familial Hypercholesterolemia Panel. *Lancet Diabetes Endocrinol.*
24 2017;**4**:850–61.
- 25 9. European Atherosclerosis Society Consensus Panel. Familial hypercholesterolaemia is
26 underdiagnosed and undertreated in the general population: guidance for clinicians to
27 prevent coronary heart disease: consensus statement of the European Atherosclerosis
28 Society. *Eur Heart J* 2013;**34**:3478–90a.
- 29 10. Pedersen KMV, Humphries SE, Roughton M, Besford JS. National Clinical Audit of the
30 Management of Familial Hypercholesterolaemia 2010: Full Report. Clinical
31 Standards Department, Royal College of Physicians, December 2010.
- 32 11. Ford I, Murray H, McCowan C, Packard CJ. Long-Term Safety and Efficacy of Lowering
33 Low-Density Lipoprotein Cholesterol With Statin Therapy: 20-Year Follow-Up of
34 West of Scotland Coronary Prevention Study. *Circulation* 2016;**133**:1073–80.
- 35 12. Braamskamp MJAM, Kastelein JJP, Kusters DM, Hutten BA, Wiegman A. Statin
36 Initiation during Childhood in Patients with Familial Hypercholesterolemia
37 Consequences for Cardiovascular Risk. *J Am Coll Cardiol* 2016;**67**:455–56.

- 1 13. Kusters DM, Avis HJ, de Groot E, Wijburg FA, Kastelein JJ, et al. Ten-year follow-up
2 after initiation of statin therapy in children with familial hypercholesterolemia. *JAMA*
3 2014;**312**:1055–7.
- 4 14. Vuorio A, Kuoppala J, Kovanen PT, Humphries SE, Tonstad S, et al. Statins for children
5 with familial hypercholesterolemia. *Cochrane Database Syst Rev* 2017;**7**:CD006401
- 6 15. Humphries SE, Cooper J, Dale P, Ramaswami U, FH Paediatric Register Steering Group.
7 The UK Paediatric Familial Hypercholesterolaemia Register: Statin-related safety and
8 1-year growth data. *J Clin Lipidol* 2017;**12**:25–32.
- 9 16. National Institute for Health and Care Excellence. Familial hypercholesterolaemia:
10 identification and management (CG71). NICE, 2008 (Last updated November
11 2017).
- 12 17. Kerr M, Pears R, Miedzybrodzka Z, Haralambos K, Cather M, et al. Cost effectiveness of
13 cascade testing for familial hypercholesterolaemia, based on data from familial
14 hypercholesterolaemia services in the UK. *Eur Heart J* 2017;**38**:1832–39.
- 15 18. Nherera L, Marks D, Minhas R, Thorogood M, Humphries SE. Probabilistic cost-
16 effectiveness analysis of cascade screening for familial hypercholesterolaemia using
17 alternative diagnostic and identification strategies. *Heart* 2011;**97**:1175–81.
- 18 19. Haralambos K, Ashfield-Watt P, Edwards R, Gingell R, Townsend D, et al. Five year
19 experience of scoring criteria for familial hypercholesterolaemia (FH) genetic testing
20 in Wales: Should the criteria be refined to include age? *Atherosclerosis* 2016;**255**:7–
21 8.
- 22 20. Mackie A, Humphries SE, Neil HAW, on behalf of the Simon Broome Register
23 Committee. Screening for familial hypercholesterolaemia in adults in the UK and the
24 UK NSC screening criteria. June 2011. Available at:
25 <https://legacyscreening.phe.org.uk/familialhypercholesterolaemia-adult>. Accessed:
26 January 2018.
- 27 21. Robson J, Dostal I, Sheikh A, Eldridge S, Madurasinghe V, et al. The NHS Health Check
28 in England: an evaluation of the first 4 years. *BMJ Open* 2016;**6**:e008840..
- 29 22. Chang K, Millett C, Soljak M, Majeed A. National coverage of the English NHS Health
30 Check programme. *Eur J Public Health* 2014;**24**:cku165-033.
- 31 23. Wald DS, Bestwick JP, Wald NJ. Child-parent screening for familial
32 hypercholesterolaemia: Screening strategy based on a meta-analysis. *BMJ*
33 2007;**335**:599–603.
- 34 24. Wald DS, Bestwick JP, Morris JK, Whyte K, Jenkins L, et al. Child–Parent Familial
35 Hypercholesterolemia Screening in Primary Care. *N Engl J Med* 2016;**375**:1628–37.
- 36 25. National Institute for Health and Care Excellence. Guide to the methods of technology
37 appraisal 2013. NICE, April 2013. Available at:

- 1 <https://www.nice.org.uk/process/pmg9/chapter/the-reference-case>. Accessed:
2 January 2018.
- 3 26. Marks D, Wonderling D, Thorogood M, Lambert H, Humphries SE, et al. Screening for
4 hypercholesterolaemia *versus* case finding for familial hypercholesterolaemia: a
5 systematic review and cost effectiveness analysis. *Health Technol Assess* 2000; 4:1–
6 123.
- 7 27. Fouchier SW, Hutten BA, Defesche JC. Current novel-gene-finding strategy for
8 autosomal-dominant hypercholesterolaemia needs refinement. *J Med Genet*
9 2015;**52**:80–4.
- 10 28. Steering Group for the Department of Health Familial Hypercholesterolaemia Cascade
11 Testing Audit Project. Family tracing to identify patients with Familial
12 Hypercholesterolaemia: the second Audit of the Department of Health Familial
13 Hypercholesterolaemia Cascade Testing Project. *Ann Clin Biochem* 2009;**46**:24–32.
- 14 29. Damgaard D, Larsen ML, Nissen PH, Jensen JM, Jensen HK, et al. The relationship of
15 molecular genetic to clinical diagnosis of familial hypercholesterolemia in a Danish
16 population. *Atherosclerosis* 2005;**180**:155–60.
- 17 30. Humphries SE, Cranston T, Allen M, Middleton-Price H, Fernandez MC, et al.
18 Mutational analysis in UK patients with a clinical diagnosis of familial
19 hypercholesterolaemia: relationship with plasma lipid traits, heart disease risk and
20 utility in relative tracing. *J Mol Med* 2006;**84**:203–14.
- 21 31. Umans-Eckenhausen MA, Defesche JC, Sijbrands EJ, Scheerder RL, Kastelein JJ.
22 Review of first five years of screening for familial hypercholesterolaemia in the
23 Netherlands. *Lancet* 2001;**357**:165–8.
- 24 32. National Clinical Guideline Centre. NICE clinical guideline CG181: Lipid modification:
25 Cardiovascular risk assessment and the modification of blood lipids for the primary
26 and secondary prevention of cardiovascular disease. Clinical Guideline Appendices.
27 NICE, July 2014 (updated September 2016). Available at:
28 <https://www.nice.org.uk/guidance/cg181/evidence>. Accessed: January 2018.
- 29 33. Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, Minhas R, et al. Predicting
30 cardiovascular risk in England and Wales: prospective derivation and validation of
31 QRISK2. *BMJ* 2008;**336**:1475–82.
- 32 34. Bhatnagar P, Wickramasinghe K, Wilkins E, Townsend N. Trends in the epidemiology of
33 cardiovascular disease in the UK. *Heart* 2016;**102**:1945–1952.
- 34 35. Office for National Statistics. Mortality statistics - underlying cause, sex and age
35 [dataset]. Available at:
36 <https://www.nomisweb.co.uk/query/select/getdatasetbytheme.asp?opt=3&theme=&su>
37 [bgrp=](https://www.nomisweb.co.uk/query/select/getdatasetbytheme.asp?opt=3&theme=&su). 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 Paediatr* 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](https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesenglandandwalesreferencetables)
18 [feexpectancies/datasets/nationallifetablesenglandandwalesreferencetables](https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/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.

- 1 48. Vuorio A, Strandberg TE, Schneider WJ, Kovanen PT. Statins and new-onset diabetes
2 mellitus - a risk lacking in familial hypercholesterolaemia. *J Intern Med*
3 2016;**279**:358–61.
- 4 49. Besseling J, Sjouke B, Kastelein JJP. Screening and treatment of familial
5 hypercholesterolemia - Lessons from the past and opportunities for the future (based
6 on the Anitschkow Lecture 2014). *Atherosclerosis* 2015;**241**:597–606.
- 7 50. Kusters DM, de Beaufort C, Widhalm K, Guardamagna O, Bratina N, et al. Paediatric
8 screening for hypercholesterolaemia in Europe. *Arch Dis Child* 2012;**97**:272-276.
- 9 51. Ritchie SK, Murphy EC, Ice C, Cottrell LA, Minor V, et al. Universal *versus* targeted
10 blood cholesterol screening among youth: The CARDIAC project. *Pediatrics*
11 2010;**126**:260–265.
- 12 52. Williams RR, Hunt SC, Barlow GK, Chamberlain RM, Weinberg AD, et al. Health family
13 trees: a tool for finding and helping young family members of coronary and cancer
14 prone pedigrees in Texas and Utah. *Am J Public Health* 1988;**78**:1283-86.
- 15 53. National Heart, Lung and Blood Institute. Expert Panel on Integrated Guidelines for
16 Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary
17 Report. *Pediatrics* 2011;**128**:S213-S256.
- 18 54. Bazian Ltd for the UK National Screening Committee. Screening for familial
19 hypercholesterolaemia in childhood: External review against programme appraisal
20 criteria for the UK National Screening Committee (UK NSC). March 2015.
21 Available at: <https://legacyscreening.phe.org.uk/familialhypercholesterolaemia-child>.
22 Accessed: January 2018.
- 23 55. Tonstad S. Familial hypercholesterolaemia: a pilot study of parents' and children's
24 concerns. *Acta Paediatr* 1996;**85**:1307–13.
- 25 56. Andersen LK, Jensen HK, Juul S, Faergeman O. Patients' attitudes toward detection of
26 heterozygous familial hypercholesterolemia. *Arch Intern Med* 1997;**157**:553–60.
- 27 57. Meulenkamp TM, Tibben A, Mollema ED, van Langen IM, Wiegman A, et al. Predictive
28 genetic testing for cardiovascular diseases: Impact on carrier children. *Am J Med*
29 *Genet A* 2008;**146A**:3136–46.
- 30 58. Sharifi M, Rakhit RD, Humphries SE, Nair D. Cardiovascular risk stratification in
31 familial hypercholesterolaemia. *Heart* 2016;**102**:1003-1008.

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1 **Legends**

2

3 **Figure 1** – Decision tree and Markov model structures.

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

8

9 (B) Markov model health states and connections. N.B. ‘Post-event’ states accessible from associated
10 event states only.

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

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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 | Akiyamen 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-) | 9.51*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 - 9.51*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 95 th percentile. | Wald et al., 2007, 2016 |
| Positive TC tests among FH- ^a | p(TC+ FH-) | 0.045 | 0.05 – (1/250) | |

^a1/250 = 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; ^cfull 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 | |

^aStaff 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); ^boriginally 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); ^cCPI used rather than health care specific index as figures available to more recent dates and higher overall, providing more conservative estimate; ^dfull 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.

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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-Eckenhuis, 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 $\geq 80\%$ 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 95 th 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 | |

^aIt 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); ^bcurrent 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); ^c80% 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); ^dfull 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

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

| | FH cases identified per 10,000 screened | | | Screening costs per diagnosis (£) | | | QALYs | Costs (£) | ICER (£/QALY) | | |
|---|---|-------|-------|-----------------------------------|-------|---------|---------|-----------|---------------------|-------------------------|-----------------------------|
| | US | RCT | total | US | RCT | total | | | 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

