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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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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. 1000 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.

1. 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

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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).

2. Materials and methods

2.1. 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.

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.

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.

2.2. Model structure and inputs

The decision tree used to model US (Fig. 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.

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