The Cost-effectiveness of Genetic Screening for Familial Hypercholesterolemia: a Systematic Review

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Abstract

Background*. Familial hypercholesterolemia (FH) is a genetic disorder that leads to elevated plasma LDL-cholesterol levels and premature coronary heart disease (CHD). An understanding of the mutations responsible for FH and the effectiveness of statins in lowering the risk of CHD in FH patients has increased interest in genetic screening strategies to improve FH diagnosis. In this study, we aimed to evaluate the cost-effectiveness of such strategies.*

Methods*. We performed a systematic review of full economic evaluations that assessed the cost-effectiveness of FH genetic screening strategies. We used relevant search terms to investigate Medline, Scopus, Web of Science, the Database of Abstracts of Reviews of Effects, the Health Technology Assessment Database, and the National Health Service Economic Evaluation Database. Data extraction and assessment of the quality of the studies were performed independently by two reviewers. The key features of the included studies are summarized in a narrative synthesis.*

Results*. We included seven economic evaluations that assessed the cost-effectiveness of genetic screening for FH, published mainly in Europe between 2002 and 2015. Most studies had a no-screening strategy as a comparator, focused on relatives of index cases with genetic or clinical diagnosis of FH (cascade screening), considered a lifetime horizon and adopted a health care payer viewpoint. Cascade screening, based on genetic testing of relatives of an index case with confirmed clinical or genetic diagnosis of FH, was shown to be cost-effective in most settings.*

Conclusions*. Our review confirms the cost-effectiveness of cascade genetic screening for the diagnosis of FH. Further research may be needed to assess the cost-effectiveness of cascade screening following the introduction of newly recommended therapeutic regimes and next-generation sequencing.*

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Introduction

Familial Hypercholesterolemia (FH) is a genetic disorder of lipoprotein metabolism that is transmitted with autosomal co-dominant inheritance and is responsible for elevated plasma low-density lipoprotein (LDL)-cholesterol (LDL-C) levels, which leads to premature coronary heart disease (CHD) and death. FH is caused predominately by LDL receptor (*LDLR*) gene variants, but mutations in apolipoprotein apoB, LDL receptor adaptor protein (*LDLRAP*) and the proprotein convertase subtilisin/kexin type 9 protein (*PCSK9*) are also known to result in FH (1). The majority of patients are heterozygotes carrying one mutated and one normal allele: patients homozygous for the same mutation in both alleles are extremely rare. A small number of patients are compound heterozygotes, with different mutations in each allele of the same gene. Patients may also be double heterozygotes with mutations in two different genes affecting LDLR function (2). The severity of the phenotype depends on the residual LDLR activity, with homozygous patients manifesting a more severe form of the disorder (1, 2).

The prevalence of the heterozygous form of FH is estimated to be between 1 in 200 and 1 in 500, with approximately 14 to 34 million people affected worldwide (3). However, it is estimated that fewer than 25% of persons with FH are diagnosed, with the majority remaining untreated or incorrectly treated (4, 5). Diagnosis of FH is currently based on clinical diagnostic criteria, mainly the Simon Broome Register or Dutch Lipid Clinic Network criteria (6, 7) with or without genetic confirmation by DNA testing (8, 9). The public health implications of the underdiagnosis of FH are significant, considering that when heterozygous FH is not treated premature atherosclerotic cardiovascular disease occurs in approximately 30% of affected women by the age of 60 and in approximately 50% of affected men by the age of 50 (8). Several studies have shown that cholesterol-lowering therapy, based mainly on treatment with statins, is effective and cost-effective in lowering the risk of CHD in heterozygous FH patients (9-12). New approaches to FH management have been proposed recently based on ezetemib and PCSK9 inhibitors (13).

The significant potential of statin treatment in reducing the risk of cardiovascular disease makes FH suitable for systematic screening according to World Health Organization (WHO) criteria (14), and several countries (Norway, Iceland, Switzerland, United Kingdom, Spain) have in fact proposed screening strategies to increase the rate of FH identification, with the Netherlands having implemented a national program in the 1990s to trace all FH patients (1). Several economic evaluations have been conducted, mainly in Europe, to assess the cost-effectiveness of different screening strategies for FH. Most of them have been summarized in a previous systematic review published in 2013 (15). Our aim is to update the previous review, with a focus on the cost-effectiveness of the genetic approach to screening for FH.

Materials and methods

This review was conducted according to the Centre for Reviews and Dissemination (University of York) guidance on undertaking systematic reviews of economic evaluations (16) and the Cochrane Handbook for systematic reviews of interventions (17).

Inclusion criteria. All economic evaluations of FH genetic testing and/or genetic screening programs were included. We included studies that used standard full economic evaluation designs such as cost-effectiveness analysis (CEA), cost-utility analysis (CUA), cost-benefit analysis, or cost-minimization analysis. Studies were

included regardless of the perspective of the evaluation (health care payer or societal perspective).

Search strategy. The literature search was performed on the following databases: Medline, Embase, Scopus, Web of Science, the Database of Abstracts of Reviews of Effects (DARE), the Health Technology Assessment (HTA) Database, and the National Health Service Economic Evaluation Database (NHS EED). It was run in July 2016. Two investigators conducted the literature search independently, to enhance sensitivity. The search terms used were: "economic evaluation OR cost-effectiveness analysis OR cost-benefit analysis" AND "familial hypercholesterolemia" AND "genetic*". The strings were adjusted for each database while maintaining a common overall architecture. The search strategy for Medline included both MeSH terms and free texts of the primary search terms. The reference lists of retrieved articles were also searched to identify potentially relevant studies.

Selection of studies. Studies were selected according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (18): after identifying relevant articles through searches of electronic databases, duplicates were removed, and titles and abstracts of the returned citations were screened. Studies that clearly did not meet the inclusion criteria were excluded. Full texts of potentially relevant articles were retrieved and independently examined by two reviewers to determine eligibility. Disagreements were resolved through discussion, and the reasons for exclusion were recorded.

Data extraction and quality assessment. Data were extracted by two reviewers independently. Data extraction focused on key methodological features (type of economic evaluation, analytical approach, study perspective, source of cost and effectiveness data, time horizon, discounting, sensitivity analyses), key characteristics of the intervention (setting, target population), and health-care pathways. Additional information, such as authors, journal, funding declaration, and year of publication, was also extracted. Quality was assessed using two tools: the BMJ checklist (19) and the Quality of Health Economic Studies (QHES) list (20). Two reviewers assessed the quality of studies using both checklists independently. Disagreement was resolved by discussion, resulting in a consensus on the quality of each study.

Data synthesis. A narrative synthesis of the studies included after eligibility checks was performed to summarize their key features and to compare study questions, interventions, methods, and results. For both CEA and CUA, the main result was usually expressed as an incremental cost-effectiveness ratio (ICER), defined as the ratio between difference in costs and difference in outcomes for two alternative interventions. ICERs were not converted into a common currency, given the specificity of each evaluation to its national setting.

Results

Seven economic evaluations that assessed the cost-effectiveness of genetic screening for FH were included in this systematic review (21-27). A flow diagram of the bibliographic search strategy used for the review is shown in Figure 1. The electronic search identified 221 studies. Ninety-three studies were duplicates and 119 were eliminated after title and abstract screening. Two full texts were excluded: a HTA report by Marks et al. (28) that included a chapter on the cost effectiveness of FH screening – this chapter was subsequently published in a paper that we had already identified (21); and an economic evaluation conducted by the same authors in 2003, which turned out to include only cost-effectiveness data for the phenotypic screening of FH (29).

Table 1 - Main features of the full economic evaluations of genetic screening for Familial Hypercholesterolemia (FH) included in this review.

First author, country and year of publication	Type of economic evaluation	Target population	Screening strategy	Comparator	ICER	Perspective	Model of analysis	Time horizon	Discounting (%)	Sensitivity analysis
Marks, UK, 2002	CEA	General population, 16-54 years	Universal screening with cholesterol and DNA test plus treatment for all FH+ cases	No screening	£78,060/LYG	Health care payer, even if not explicitly stated	Decision-tree model and life-table analysis	Lifetime	6 (costs) 1 (effectiveness)	Deterministic (one-way)
		Young people, 16 years	Universal screening with cholesterol and DNA test plus treatment for all FH+ cases	No screening	£14,842/LYG					
		Patients consulting for unrelated reasons in primary care, 16-54 years	Opportunistic screening with cholesterol and DNA test plus treatment for all FH+ cases	No screening	£70,009/LYG					
		Patients admitted to hospital with premature myocardial infarction, 16-54 years	Opportunistic screening with cholesterol and DNA test plus treatment for all FH+ cases	No screening	£21,106/LYG					
		First degree relatives of people with diagnosed FH	Cascade screening with DNA test plus treatment for all FH+ cases	No screening	£4,914/LYG					
Marang-van de Mheen, Netherlands, 2002	CEA	First and second degree relatives of index cases with FH and a LDLR gene mutation aged ≥ 16	Cascade screening with DNA test plus treatment for all FH+ cases	No screening	€31,260/LYG	Health care payer, even if not explicitly stated	Cohort life-table model	Lifetime	Not applied	Deterministic (one-way)
			Cascade screening with DNA test plus treatment for untreated FH+ cases	No screening	€32,164/LYG					
			Cascade screening with DNA test plus treatment for FH+ cases with elevated cholesterol levels	No screening	€29,918/LYG					
			Cascade screening with DNA test plus treatment for untreated FH+ cases with elevated cholesterol levels	No screening	€30,843/LYG					
			Cascade screening with DNA test plus treatment for FH+ cases with CBO criteria	No screening	€25,613/LYG					
			Cascade screening with DNA test plus treatment for untreated FH+ cases with CBO criteria	No screening	€27,700/LYG					

Study	Analysis	Population	Intervention	Comparator	ICER	Perspective	Model	Time horizon	Discount rate (%)	Sensitivity analysis
Wonderling, Netherlands, 2004	CEA	Relatives of index cases with FH and a LDLR gene mutation	Cascade screening with DNA test plus treatment for untreated FH+ cases	No screening	$8,800/LYG	Health care payer, even if not explicitly stated	Life-table analysis	Lifetime	4	Deterministic (one-way and bounded)
Oliva, Spain, 2009	CEA	First degree relatives of an index case with FH and a LDLR gene mutation	Cascade screening with DNA test plus treatment for all FH+ cases	No screening	€3,423/LYG	Health care payer	Life-table analysis	Lifetime	3	Deterministic (one-way) and probabilistic
Nherera, UK, 2011	CUA	A cohort of 1000 people suspected of having FH aged 50 years for index cases and 30 years for relatives (first degree)	Cascade screening with DNA test for relatives of all index cases plus treatment for all FH+ cases	Cascade screening with LDL test for relative of all index cases	£479/QALY	Health care payer	Decision tree plus Markov model	Lifetime	3.5	Deterministic (one-way) and probabilistic
			Cascade screening with DNA test for relatives of FH+ cases OR LDL test for relatives of DFH cases without genetic mutation plus treatment for all FH+ cases		ED					
			Cascade screening with DNA test for relatives of FH+ cases OR with LDL test for relatives of DFH/PFH cases without genetic mutation plus treatment for all FH+ cases		£3,666/QALY					
Ademi, Australia, 2014	CEA and CUA	First- and second-degree relatives of probands with genetically confirmed FH. (42 years in first cycle of the Markov model)	Cascade screening with DNA and LDL test plus treatment for all FH+ cases	No screening	AU$4,154/LYG; AU$3,565/QALY	Health care payer	Decision tree plus Markov model	10 years	5	Deterministic (one-way and bounded) and probabilistic
Chen, USA, 2015	CUA	Male adults, relatives of an index case with clinical diagnosis of FH	Cascade screening with DNA test plus treatment for FH+ cases OR LDL-C test every 2 years if no mutation	Cascade screening with LDL-C test plus statin treatment OR repeat LDL-C test every 2 years	$519,813/QALY	US societal perspective	Decision tree plus Markov model	Lifetime	3	Deterministic (one-way) and probabilistic

CEA: cost-effectiveness analysis; CUA: cost-utility analysis; FH+: people with genetic mutation diagnostic for familial hypercholesterolemia; CBO: Dutch Institute for Healthcare Improvement criteria for initiation of lipid-lowering therapy (based on the risk of cardiovascular disease); DFH: definite FH; PFH: possible FH; ED: extendedly dominated; ICER: incremental cost-effectiveness ratio; LYG: life year gained; QALY: Quality-adjusted life year gained

Table 2 - Main assumptions used in the full economic evaluations of genetic screening for Familial Hypercholesterolemia (FH) included in this review.

First author, country and year of publication	Type of health costs considered						FH prevalence	Accuracy of screening test	Treatment regime (daily)*	Statins efficacy	Quality score (QHES) list
	Organization of screening	Consultation (clinical/genetic)	Screening test (clinic/genetic)	Treatment	Follow up visits	Disease costs (cardiovascular events prevented)					
Marks, UK, 2002 (21)	yes	yes	yes	yes	no	yes	3.8% (universal screening) to 95% (cascade screening)	Not reported	70% simvastatin 40 mg and 30% atorvastatin 20 mg	Not reported (based on Simone Broome's cohort data)	90
Marang-van de Mheen, Netherlands, 2002 (22)	yes	yes	yes	yes	yes	no	34% FH+/2,229 screened	Not reported	50% atorvastatin, 45% simvastatin, 5% pravastatin	21% reduction in total cholesterol; 5% increase in HDL cholesterol	87
Wonderling, Netherlands, 2004 (23)	yes	yes	yes	yes	yes	yes	Not reported	Not reported	simvastatin from 10mg to 40 mg pravastatin from 10 mg to 40 mg atorvastatin from 10 mg to 60mg	Life expectancy with statin treatment 70.6 (male aged 20) to 82.3 (female aged 20) Life expectancy without statins 65.5(male) to 77.2 (female)	96
Oliva, Spain, 2009 (24)	no	no	yes	yes	yes	yes	50%	DNA test 99.7% specificity and 99.9% sensitivity	40 mg simvastatin or 40 mg atorvastatin	Not reported (based on Simone Broome's cohort data)	85
Nherera, UK, 2011 (25)	yes	yes	yes	yes	no	yes	48%	DNA test 100% sensitivity and specificity	2% simvastatin 40mg 9% simvastatin 80mg 64%atorvastatin 80mg 4% simvastatin 40mg + ezetimibe 11% simvastatin 80mg + ezetimibe 10% atorvastatin 40mg + ezetimibe	Relative Risks statins vs non statins: Myocardial infarction 0.81 Stroke 0.82 Peripheral artery disease 0.87 Heart failure 0.77 Revascularization 0.78 Unstable angina 0.84 Cardiovascular death 0.92 Death other causes 1.00	100

The main features of the seven economic evaluations identified are summarized in Table 1. They were published between 2002 and 2015, five in Europe (UK, Netherlands, Spain) (21-25), one in Australia (26) and one in the USA (27). Only the three most recent studies used CUA (25-27), while the others used CEA (21-24). Three studies assessed genetic screening alone (22-24), while four assessed a combination of genetic and phenotypic screening (21, 25-27). Most studies had a no-screening strategy as a comparator (21, 22-24, 26), and all studies focused on relatives of index cases with genetic or clinical diagnosis of FH (cascade screening), but one study also included general population and opportunistic screening strategies (21). The majority of studies modeled hypothetical screening programs (21, 24-27), while two aimed to evaluate the cost-effectiveness of existing screening programs (22, 23). The time horizon was lifetime in the majority of the studies (21-24, 27), but in one case it was 10 years (26). The adopted viewpoint was health care payer in all but one study, which used a societal perspective (27).

The costs included in the evaluations reflect the viewpoint of the analysis, with all studies focusing only on direct health costs but one, where the patient-time lost per physician visit was included as a type of indirect cost (27). Table 2 summarizes the main categories of health costs, including the other assumptions adopted to build the economic models, and reports the quality scores of the economic evaluations. The quality of the economic evaluations retrieved was quite high, although in some cases there was a lack of justification for the type of evaluation adopted and the incremental analysis was poorly described (21-24). In the narrative description of each study, we report only the results of the QHES tool, which provides a quantitative synthesis of the study quality. Evaluations made using Drummond's BMJ tool were consistent
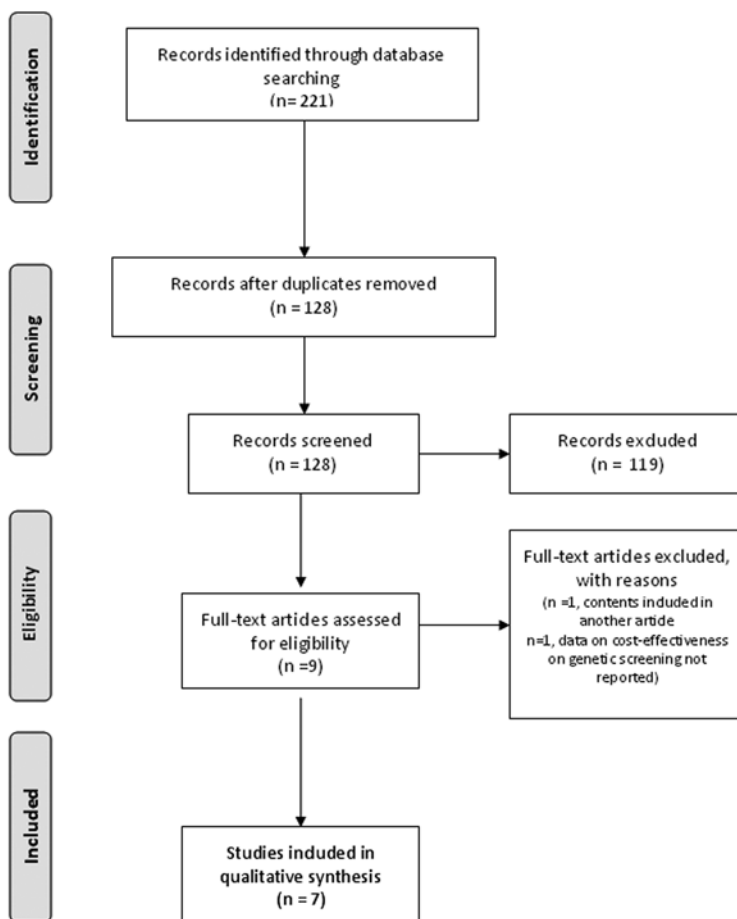
Study								Test	Treatment	Outcome	Quality score
Ademi, Australia, 2014 (26)	no	no	yes	yes	yes	yes	no	54.3%	DNA test 100% sensitivity and specificity	Atorvastatin 40 mg daily (50%) and atorvastatin 80 mg daily (50%)	76% reduction in risk of CHD among FH	97
Chen, USA, 2015 (27)	yes	yes	yes	yes	yes	yes	yes	Not reported	DNA test 78.5% sensitivity LDL-C test 91% sensitivity	Atorvastatin 10mg	Decrease in total cholesterol 28.0% (25.9–30.1) Decrease in LDL cholesterol 38.0% (35.7–40.3) Increase in HDL cholesterol 5.5% (2.75–8.25)	100

*Percentages indicate the distribution of different treatment regimes in the models used for the economic evaluations

Figure 1 -. Flowchart of the electronic search

with those obtained through Chiou's QHES scores (data not shown), the latter of which ranged from 85 to 100 (Table 2).

In 2002 Marks et al. published a cost-effectiveness analysis of a modeled screening program for FH in the UK, which had previously been included in a HTA report (28). The authors compared three different screening strategies (universal, opportunistic and cascade) to no-screening in five population groups, through a combination of life-table and decision-tree models with a lifetime horizon (21) (Table 1). In their model, both the universal and opportunistic strategies involve the measurement of non-fasting cholesterol, followed by a fasting test when the non-fasting concentration is above the population 95th percentile, and by genetic confirmation of FH if fasting cholesterol levels are above 7.5 mmol/L and LDL cholesterol above 4.9 mmol/L Universal screening according to this diagnostic pathway was used for both the general population aged 16-54 and (separately) for a sub-population of 16 year-olds; the opportunistic screening approach was used either for patients aged 16-55 years who presented for unrelated primary care or for patients admitted to hospital with premature myocardial infarction. The

third strategy evaluated by Marks et al. (28) was cascade screening, which targets first degree relatives of people with a confirmed diagnosis of FH; it involves gathering family history data and performing genetic tests of the proband and relatives to uncover the prevalence of the known mutation within the family. For confirmed cases of FH, all three strategies envisage the initiation of statin therapy with either simvastatin (40 mg daily) or atorvastatin (20 mg daily) (Table 2). The effect of statin treatment was derived from the Simon Broome Registry data (6) (Table 2). Outcomes were only modelled for the age range 16 to 54 years, since, according to the authors, there are no clinical endpoint data to support the effectiveness of statin treatment in older individuals (28). The underlying prevalence of FH in the model ranged from 3.8% for the universal screening approach to 95% for cascade screening (Table 2). Outcome data were also derived from the Simon Broome cohort (6). Probabilities of attendance for the different stages of screening (cholesterol and DNA tests) and of adherence to treatment were also included in the model. Discount rates of 6% for costs and 1% for effectiveness were applied (Table 1). The estimated ICER ranged from £4,914 per year of life gained (LYG) for cascade screening to £78,060/LYG for universal screening in which all people aged 16-54 were targeted (Table 1). The sensitivity analysis did not change the rank of alternatives, confirming cascade screening as the most cost-effective screening approach. The study, which has a quality score of 90 using Chiou's scale (Table 2), has some methodological limitations, such as the lack of incremental analysis for all proposed strategies.

Marang-van de Mheen et al. examined the cost-effectiveness of the Dutch genetic cascade screening program compared to a no-screening strategy using a cohort life-table model with a lifetime horizon (22) (Table 1). First and second degree relatives

of probands with genetic diagnosis of FH were offered genetic tests and treated with statins (atorvastatin, simvastatin or pravastatin) on the basis of six alternative eligibility strategies: (a) treat all individuals with a FH mutation; (b) treat all individuals with a FH mutation and elevated cholesterol levels; (c) treat all individuals with a FH mutation fulfilling the Dutch Institute on Health Care Improvement (CBO) consensus guideline criteria; (d) treat individuals with a FH mutation only if untreated at the time of screening; (e) treat individuals with a FH mutation and elevated cholesterol levels only if untreated at the time of screening; (f) treat individuals with a FH mutation fulfilling the CBO consensus guideline criteria only if untreated at the time of screening. The statin effect was derived from a meta-analysis of randomized controlled trials (RCTs) reporting a 21% reduction in total cholesterol and a 5% increase in HDL cholesterol (30); the prevalence of FH among relatives was 34% (Table 2). The estimated ICER ranged from € 25,613 to € 32,164 per LYG depending on the treatment strategy and exceeded the cut-off point of €1 8,151 per LYG set by the Dutch cholesterol consensus guidelines (22) (Table 1). One-way sensitive analysis did not change these results. The perspective adopted is not clearly stated and costs and benefits are not discounted. The study has some methodological limitations and its quality score is 87.

The cost-effectiveness of the Dutch cascade screening program for FH was also assessed by Wonderling et al. using a life-table model, based on the actual data from the national program for the year 2000 (23) (Table 1). The cascade screening strategy, as described by Marang-van de Mheen et al. (22), was compared to no-screening, in a model where all untreated diagnosed cases of FH initiate treatment with statins (different daily doses of simvastatin, pravastatin or atorvastatin, based on the actual distribution of treatment regimes in the Dutch national

program) from 18 to 60 years of age. It was assumed that 82% of those not already on statins would be prescribed them after diagnosis. In contrast to the previous analysis conducted in the Netherlands, the effectiveness of statins and life expectancy data were derived from the Simon Broome Registry (6) (Table 2). A discount rate of 4% per year was applied to both costs and outcomes (Table 1). The estimated underlying prevalence of FH was not stated. Considerations relating to adherence to treatment and to accuracy of the genetic test were lacking. In this model, the estimated ICER of cascade screening compared to no-screening was $8,800/LYG (Table 1). The quality score of the study is 96.

Oliva et al. conducted a cost-effectiveness analysis of genetic cascade screening for first-degree relatives of patients with FH compared to no-screening, performing a life-table analysis with a lifetime horizon from the perspective of the Spanish National Health System (24). Life-tables were built on a cohort of 503 patients under 60 years included in a pilot study conducted by the Familial Hypercholesterolemia Foundation in Spain, applying statin effectiveness data from the Simon Broome cohort (6) and age- and sex-adjusted life-expectancy data from the Spanish National Statistics Institute (INE). Health benefits were not applied to patients aged over 60. In the pilot study used to build the model, index cases received both clinical and genetic diagnosis of FH, where genetic testing was performed using a platform that included the most frequent *LDLR* mutations in Spain, with a specificity and sensitivity of 99.7% and 99.9%, respectively (Table 2). In the proposed screening strategy, first-degree relatives are tested for the identified mutation and all diagnosed cases are offered statin treatment (a daily dose of 40 mg/day simvastatin or atorvastatin was included in the model). The prevalence of FH among relatives of index cases was assumed to be 50% (Table 2). A discount rate of 3% was adopted. The estimated ICER of cascade screening compared to no-screening was € 3,423/LYG (Table 1). The sensitivity analysis showed a significantly higher ratio only in the case where all patients were treated with atorvastatin. Probabilistic analysis showed that the screening program was better than the alternative at a probability level of 95%, considering a threshold of € 7,400/LYG. The model adopted is not well described in the paper, and the quality was rated 85/100.

Nherera et al. built a Markov model to establish the cost-effectiveness of different cascade screening strategies, which involved measuring blood cholesterol levels, or performing a genetic test, or both, from a health care payer point of view and with a lifetime horizon (25) (Table 1). Starting from a cohort of 1,000 people suspected of having FH, aged 50 years for index cases and 30 years for first degree relatives, four cascade screening strategies were compared: cascade screening with LDL cholesterol testing of relatives of all index cases with definite (DFH) or possible (PFH) FH (FH+); cascade screening with DNA testing of relatives of all index cases with a causative mutation (FH+); cascade screening with DNA testing of relatives of index cases with a causative mutation (FH+) and LDL cholesterol testing of relatives of DFH index cases without causative mutation; and cascade screening with DNA testing of relatives of index cases with a causative mutation (FH+) and LDL cholesterol testing of relatives of DFH and PFH index cases without causative mutation. All DFH/PFH index cases and relatives are offered high-intensity statin therapy (simvastatin or atorvastatin ± ezetimibe). The statin effect was derived from a meta-analysis of RCTs performed by the authors (25). The model used a prevalence of FH among relatives of 48% and a DNA testing sensitivity and specificity of 100% (Table 2). A discount rate of 3.5% was applied to costs and benefits. The ICERs were calculated

from a comparison of the strategies with each other rather than with a no-screening control (Table 1). The ICER for cascade screening with DNA testing for relatives of all index cases compared to cascade screening with cholesterol testing was £ 479 per quality-adjusted life year (QALY) gained. Cascade screening comprising DNA testing combined with LDL testing in relatives of DFH index cases without mutation was extendedly dominated (ED). Therefore the following incremental comparison was made between cascade screening with DNA testing for relatives of FH+ index cases combined with LDL testing in relatives of DFH/PFH index cases without mutation and cascade screening with DNA testing of all index cases, resulting in an ICER of £3,666 per QALY gained (Table 1). According to the authors, this last strategy was the most cost-effective as it fell below the recommended £20,000/QALY threshold currently used in the UK (25). The probabilistic sensitivity analysis confirmed this scenario. The study methods and reporting of results are good, resulting in a quality score of 100, even though effectiveness data are not well reported.

Ademi et al. constructed a 10-year time horizon Markov model to determine the cost-effectiveness of a genetic cascade screening program supplemented with cholesterol testing compared to a no-screening strategy from a health care payer perspective (26) (Table 1). This study is the only one to provide details of the no screening strategy's costs, including disease costs and intervention costs (26). First- and second-degree relatives of probands with genetic diagnosis of FH were offered genetic and cholesterol testing and statin treatment (atorvastatin) if FH positive. The benefits of statin treatment were derived from a cohort study of Dutch FH patients, which demonstrated an overall reduction in risk of CHD of 76% (31); prevalence of FH among the population screened was assumed to be 54.3%, while

DNA testing sensitivity and specificity were assumed to be 100% (Table 2). A discount rate of 5% was applied to costs and benefits (table 1). The ICER in Australian dollars was AU$4,155/LYG and AU$3,565/QALY, under the cut-off point of AU$15,000 to AU$45,000 considered cost-effective in Australia (Table 1). Probabilistic sensitivity analysis confirmed the cost-effectiveness in more than 99% of simulations. The QHES score of 97 reflects the high quality of the study.

Finally, Chen et al. conducted a cost-utility analysis based on a combination of decision tree and Markov model that compared a genetic screening strategy for FH in the USA with the currently recommended lipid screening strategy for individuals with high cholesterol and a family history of FH or heart disease (27) (Table 1). The analysis was based on a cohort of 1,000 male adults with a family history of FH and high-risk baseline cholesterol levels. It had a lifetime horizon and was conducted from the US societal perspective including some indirect costs and estimating utilities from several studies. The proposed genetic cascade screening strategy includes performing the DNA test of a proband with clinical diagnosis of FH to look for *LDLR* or *APOB* gene mutations and a genetic test in relatives, followed by statin treatment with 10 mg atorvastatin daily for confirmed cases of FH (Table 2). The sensitivity of the DNA tests was estimated to be 78.5% (Table 2). For those without a mutation, the strategy envisages repetition of an LDL-C test every two years and initiation of statin treatments for LDL-C levels above 190 mg/dL. The lipid cascade screening currently recommended in the USA is based on an LDL-C test in relatives of an index case with clinical diagnosis of FH, with a 91% sensitivity, repeated every two years. The discount rate applied was 3% (Table 1). The ICER of the genetic screening compared to the lipid screening was $519,813/QALY (Table 1), which falls

above the US willingness-to-pay threshold of $150,000/QALY. Sensitivity analyses showed that results were robust to variations in model parameters. The methods and the reporting of results are very good, giving a quality score of 100.

Discussion and conclusions

Our systematic review shows that cascade screening based on genetic testing of relatives of an index case with confirmed clinical or genetic diagnosis of FH is cost-effective in most settings. In particular, taking as a reference the National Institute for Clinical Excellence (NICE) willingness-to-pay threshold (£ 20,000–30,000/QALY or LYG) (32) and the thresholds used in the United States ($50,000–100,000/QALY or LYG) (33), all but one study showed a favorable ICER for cascade screening. The exception is the economic evaluation conducted by Chen et al. in the USA, with an estimated ICER of $ 519,813/QALY for genetic screening compared to the currently recommended lipid screening strategy (27). The lack of cost-effectiveness in this economic evaluation is mainly attributable to the high cost of genetic testing in the USA: FH genetic testing kits validated in European countries, used in the other studies, have not been validated in the US, where the common mutations may differ from those identified in Europe (27). Furthermore, as stated by the authors, most European studies present ICER results for genetic screening compared to a no-screening control, rather than lipid screening, which probably overestimates the effectiveness of genetic screening (27).

Marang-van de Mheen et al. concluded that the range of cost-effectiveness ratio values for cascade screening, based on different treatment strategies, exceeded the cut-off point of €18,151/LYG given by the Dutch cholesterol consensus guidelines (22). In particular, the authors made a call

regarding the reduction in the cost of statin treatment, being the single most important determinant of costs. In contrast, the cost-effectiveness analysis subsequently performed by Wonderling et al. resulted in a much more contained ICER ($8,800/LYG), which falls below the cut-off point set at the national level (23). The two research groups made different assumptions to build their models; for example, while Wonderling et al. used actual mortality rates in FH patients, based on the Simon Broome cohort (6), Marang-van de Mheen et al. used mortality data from the Framingham study, which are not specific for FH patients (34). Furthermore, while Wonderling et al. adopted discounting conventions that generated substantial differences, Marang-van de Mheen et al. did not. In addition, the latter research group included children in the screening strategy, modelled for reduced drug compliance and used prescription data from clinical practice (23). Marang-van de Mheen et al. assumed that treatment costs and effects of statins would continue up to the age of 85, while Wonderling et al., like all other cost-effectiveness analyses (21, 24), modelled statin efficacy only up to 60 years of age. Data from the Simon Broome cohort have in fact shown in FH patients above 60 years of age a similar mortality and longevity to the general population, suggesting that statins have a limited health benefit in this age group (6).

One of the main limitations of the available evidence on the cost-effectiveness of genetic screening for FH is that most published evaluations lack a direct comparison between the genetic and the phenotypic approach to screening for FH: five of the seven economic evaluations used no-screening as a comparator (20-23, 25), while only Nehera et al. (25) and Chen et al. (26) compared the cost-effectiveness of genetic testing with a cholesterol screening method. Marks et al. and Marang-van de Mheen et al. evaluated the cost-effectiveness of both lipid and

genetic screening strategies, but they did not compare the two strategies with each other (21, 22). Some authors justified not comparing genetic with lipid screening by pointing to the low specificity and sensitivity of LDL-C testing, arguing that it is not of a sufficiently high standard for diagnosis of FH (23, 24). Indeed, data from the national FH screening program in the Netherlands showed that LDL-C may lead to a diagnostic error rate of 17% in carriers of a single functional mutation (35). There is also evidence that LDL testing is a poor predictor of FH in family members: data from a Danish cohort showed that nearly a quarter of relatives with a mutation have levels of LDL-C which are below the 90th percentile (36). On the other hand, some authors have argued that genetic screening can offer false reassurances to variant-negative patients who might be at risk (37). It has to be noted, in fact, that current DNA testing for FH is not 100% sensitive because the disorder may be caused by an unknown genetic mutation. Therefore, not finding a mutation does not necessarily exclude a diagnosis of FH (38). There is evidence that approximately 15% of people with confirmed clinical diagnosis of FH do not have a mutation in their *LDLR*, *APOB* or *PCSK9* genes (with estimates ranging from 12% to 48%) (39). Given the existing controversies regarding the choice of the screening test (genetic or lipid), further research to directly compare the cost-effectiveness of these two methods may be needed.

Despite the fact that comparing a genetic screening strategy to no population screening rather than to alternative strategies (such as lipid screening) may drive up the effectiveness of FH genetic screening (27), we believe that the published economic evaluations are likely to underestimate the actual cost-effectiveness of genetic screening for FH, mainly because of the following factors: underestimation of statin efficacy in the models, choice of the therapeutic regime included in the models, choice of the target population, and type of genetic tests included.

Four studies estimated the effects of statin therapy on cholesterol levels from a cohort study. Marks et al. (21), Wonderling et al. (23) and Oliva et al. (24) referred to the Simon Broome Register, a UK cohort of 1,185 patients with heterozygous FH followed prospectively from 1980 to 1995 and treated mainly with statins from 1992 until completion of the analysis, which was published in 1999 (9). The patients of this cohort were generally treated with lower doses than those indicated today. Therefore, in these studies, the health benefits of statin treatment may have been underestimated. Ademi et al. (26) referred to a Dutch cohort study published in 2008 that determined the efficacy of statin treatment on risk of coronary heart disease in patients with FH from 1990 to 2002 (31); they claimed that this was the only study addressing a FH population with characteristics comparable to their own study population. Two studies based the effects of statins on a meta-analysis of trials: Marang-van de Mheen et al. (22) referred to a meta-analysis published in 1999, which included five trials published between 1994 and 1998, and which estimated statin efficacy particularly in elderly individuals and women (30); Nherera et al. (25) themselves performed a meta-analysis of four trials published between 2004 and 2005, and compared high-intensity statins with low-intensity statins after myocardial infarction. In both cases, the population from which estimates were taken was not a FH population. Finally, Chen et al. (27) referred to a 2008 narrative review that summarized the clinical efficacy of the various statins, with a particular focus on rosuvastatin (40), and to two short trials published in 1998 (41) and 2003 (42), which compared the efficacy of different statins at reducing LDL-cholesterol in patients with hypercholesterolemia. Neither of these

studies specifically addressed FH patients, thus also possibly underestimating efficacy data included in their model.

Statin therapy was the only treatment considered in all studies, with the exception of Nehera et al., which also included ezetimibe (25). The statin treatment protocols evaluated employ heterogeneous drug and dosage regimes and most of them do not comply with recognized guidelines. European and American guidelines recommend starting treatment with high-intensity regimes (3, 8, 9) involving either 80 mg atorvastatin, 40 mg rosuvastatin or 4 mg pitavastatin. A regime with 80 mg simvastatin is not advocated as this dose is associated with elevated risk of myositis and rhabdomyolysis (3, 9). Most published evaluations do not comply with these regimens; for example, Chen et al. include a protocol with the lowest dose of statin (10 mg atorvastatin) in their study (27), which is justified on the basis of minimizing the risk of medication-related side effects. It remains uncertain whether adopting a higher dose would have improved the cost-effectiveness of their model. Furthermore, statin therapy alone might not be sufficient to attain cholesterol targets, which is why recent guidelines consider alternative drugs for the treatment of adults with primary heterozygous FH. For example, NICE and European Atherosclerosis Society guidelines recommend ezetimibe as a second line and bile acid binding resins as a third line (3, 8), in agreement with the American Heart Association guidelines, which also consider PCK9 inhibitors as a third line therapy (9). These new and better optimised pharmaceutical treatments will need to be considered in future economic analyses to provide a more realistic assessment of cost-effectiveness.

Although the guidelines mentioned (3, 8, 9) recommend the screening and treatment of children starting at age 8-10, children were not considered in the economic evaluations retrieved. Most studies did not include children under the age of 16 in the screening programs (21, 22, 25-27) and those that did include children did not treat them until the age of at least 18 (23, 24). This was justified by pointing to the lack of data on the effectiveness of statins in children. We might suppose that inclusion of children is likely to increase the cost-effectiveness of screening programs as the number of relatives per index case would increase and consequently the health benefits.

Finally, although the exact type of genetic testing included in the models is specified only by Oliva et al. (DNA array followed by quantitative PCR), it is likely that the use of arrays and/or PCR amplification was included in all studies when estimating the costs of genetic testing. However, the introduction of next generation sequencing (NGS) has been estimated to be able to reduce the cost of FH testing by as much as four-fold (43). Evidence on the effectiveness of NGS is promising, demonstrating higher levels of specificity and sensitivity in detecting FH, in particular when combined with clinical criteria (44, 45). Thus, further studies on the cost-effectiveness of genetic screening for FH should be conducted based on the adoption of NGS techniques.

In conclusion, our review confirms the cost-effectiveness of cascade genetic screening for the management of FH. Indeed, the assumptions used to build the models may even underestimate the actual cost-effectiveness of this approach, in view of the therapeutic regimes currently recommended and of new technologies developed for genetic testing. Further research may therefore be needed to assess the cost-effectiveness of cascade screening based on treatment schemes that extend beyond statin treatment alone, and on the introduction of NGS for genetic diagnosis. More data may also be needed to directly compare the cost-effectiveness of genetic vs. lipid screening of FH or a combination of both approaches. Given the high percentage

of FH cases that cannot be diagnosed with the currently identified mutations in the *LDLR*, *APOB* and *PCSK9* genes, a strategy that combines genetic and phenotypic testing may currently guarantee the highest level of accuracy, although data directly comparing this strategy to genetic screening are scarce.

Riassunto

Costo-efficacia dello screening genetico per l'Ipercolesterolemia familiare: una revisione sistematica.

Introduzione. L'ipercolesterolemia familiare (IF) è una malattia genetica che determina elevati livelli di colesterolo LDL nel plasma e rischio aumentato di malattia coronarica precoce (CHD). Le nuove conoscenze sulle mutazioni responsabili dell'IF e la dimostrata efficacia delle statine nel ridurre il rischio di malattia coronarica in questi pazienti hanno sollevato interesse per le strategie di screening genetico in grado di aumentarne la diagnosi. L'obiettivo del nostro lavoro è quello di valutare la costo-efficacia di tali strategie.

Metodi. Abbiamo eseguito una revisione sistematica di valutazioni economiche complete che valutassero la costo-efficacia di strategie di screening genetico per l'IF. Avvalendoci degli appropriati termini di ricerca abbiamo interrogato Medline, Scopus, Web of Science, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database e National Health Service Economic Evaluation Database. L'estrazione dati e la valutazione della qualità degli studi inclusi sono state eseguite indipendentemente da due ricercatori. Le caratteristiche chiave degli studi inclusi sono state sintetizzate con un approccio narrativo.

Risultati. Sono state incluse sette valutazioni economiche incentrate sulla costo-efficacia dello screening genetico per l'IF, pubblicate tra il 2002 e il 2015 principalmente in Europa. La maggior parte degli studi ha utilizzato la strategia "no screening" come comparatore per la valutazione, si è focalizzata su parenti di casi indice con diagnosi genetica o clinica di IF (screening a cascata), ha utilizzato un orizzonte temporale lifetime e una prospettiva sanitaria. Lo screening genetico a cascata sui parenti di un caso indice confermato con diagnosi clinica o genetica è risultato costo-efficace nella maggior parte dei casi.

Conclusioni. La nostra revisione conferma la costo-efficacia dello screening genetico a cascata per la diagnosi dell'IF. Ulteriori ricerche sono necessarie per valutare l'impatto dei nuovi farmaci e delle nuove tecniche di sequenziamento genico disponibili sulla costo-efficacia dello screening a cascata.

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