Journal of Clinical Lipidology (2017) 11, 260–271

Journal of Clinical Lipidology

Cost-effectiveness of a cascade screening program for the early detection of familial hypercholesterolemia

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KEYWORDS:
Familial hypercholesterolemia;
Cost-effectiveness;
Cardiovascular disease;
Cascade screening program

BACKGROUND: Although familial hypercholesterolemia (FH) confers a high risk of coronary artery disease, most patients are undiagnosed, and little is known about the efficiency of genetic cascade screening programs at national level.

OBJECTIVE: The aim of the study was to estimate the cost-effectiveness of a national genetic cascade screening program in Spain.

METHODS: An economic evaluation was performed using a decision tree analysis. The choice in the decision tree was between implementation of the national program for FH (NPFH) or keeping the usual clinical care. The NPFH detects FH patients through total cholesterol measurement at primary care level and use of genetic testing in index cases and relatives. The payer (National Health System) and social (including the productivity lost) perspectives were considered. The outcome variables were coronary events avoided, deaths avoided, and quality-adjusted life years (QALYs) gained.

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Submitted November 21, 2016. Accepted for publication January 2, 2017.

http://dx.doi.org/10.1016/j.jacl.2017.01.002

RESULTS: From the payer perspective, the application of the NPFH during 1 year prevents 847 coronary events and 203 deaths in the 9000 FH patients cohort during a 10-year follow-up, yielding an extra 767 QALYs, at a cost of €29,608 per QALY gained. From the social perspective, the NPFH is dominant over the control (the cost decreases and the effectiveness increases). The sensitivity analysis confirms the robustness of the findings.

CONCLUSION: The NPFH based on molecular testing is a cost-effective diagnostic and management strategy that supports government expenditure aimed at preventing coronary artery disease in FH patients in Spain. Implementation of such a strategy is likely to be also cost-effective in countries with similar developed healthcare systems.

Introduction

Heterozygous familial hypercholesterolemia (FH) is a common genetic disorder, which results in lifelong elevation of low-density lipoprotein-cholesterol (LDL-C). The causative mutations are mainly in genes affecting the low LDL receptor. Recent data suggest that the prevalence of FH ranges from 1 in every 250 to 300 people worldwide.[1,2] Thus, more than 130,000 people may have the disorder in Spain.[3] FH is associated with the development of premature atherosclerosis cardiovascular disease (ASCVD), especially coronary artery disease (CAD). It has been shown that 50% of men and 20% of women with heterozygous FH who do not receive suitable treatment will suffer an acute coronary episode by their 50s.[1–3] Mortality rates have decreased, however, since statins were introduced into clinical practice.[4]

Although recent guidelines for the management of FH highlight the high associated CAD risk, most patients with FH remain undiagnosed and untreated.[1,2] From the public health perspective, a valuable strategy for covering this gap in diagnosis and treatment of FH is the implementation of a family-based cascade screening program with the participation of primary care (PC) physicians and specialist centers or lipid clinics. Several studies have shown that the most cost-effective preventive strategy is that of screening the close relatives of individuals diagnosed with FH.[2,5–7] A recent systematic review of economic evaluations of the detection and treatment of FH concludes that cascade screening for new cases of FH appears to be cost-effective, but there are uncertainties especially with regard to the underlying prevalence of FH, validity of the screening tests, and use of different approaches to assess the outcomes of treatment. The authors recommend to perform economic evaluations with country-specific data.[8]

However, few countries to date have implemented a national strategy based on genetic cascade screening. The SAFEHEART (Spanish Familial Hypercholesterolemia Cohort Study) registry has carried out a successful family-based cascade screening program that may be useful as a pilot study for the development of a national program.[9,10] Assuming that about 25% FH patients in Spain have been detected, approximately 90,000 patients remain undetected.[3]

The aim of this study was to assess the efficiency, in terms of cost/effectiveness and cost/utility, of a national genetic screening program implementation for FH compared with no implementation in Spain.

Materials and methods

Design

According to the national program for FH (NPFH), FH cases are detected at PC level.[3] The economic evaluation was performed using a decision tree with deterministic sensitivity analysis. The choice in the decision tree was the implementation of the NPFH or keeping the usual clinical practice. This structure simulates a prospective cohort study.

Two perspectives were considered: the payer perspective, that is, the National Health System (NHS) considering only direct costs, and the social perspective, considering both direct and indirect costs (work productivity lost because of illness). The NPFH was applied 1 year, and the costs and outcomes were estimated for a time horizon of 10 years. A 3% annual discount rate was applied.[11]

Sources of information: Evidence and expert opinion

The Spanish FH Foundation convened a scientific committee (SC) acting as a national experts panel, comprised of 8 specialists in lipidology and cardiology (P.M., R.A., L.P., O.M., F.J.F., J.L.M., J.L.D., and J.R.G.J.), and an expert international panel (G.W. and R.N.). Activities and meetings were coordinated and chaired by P.M. The panel collected relevant articles through a MEDLINE search. The SC worked from January to December 2015, met twice, and worked thereafter electronically to give estimators in case of insufficient or contradictory evidence. The SC members answered questions related to the model variables to obtain the needed data as model inputs. Rather than force a consensus, the distribution of the answers was considered for the sensitivity analysis.

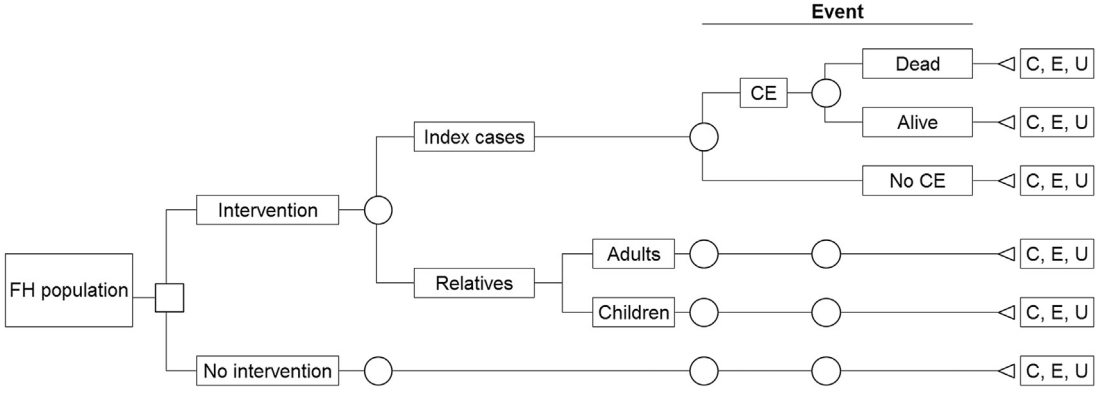
Model building

To build the decision tree, the NPFH was modeled with the following assumptions: (1) The index case (IC) detection strategy is aimed at adults with total cholesterol (TC) > 300 mg/dL who came to PC; (2) the screening strategy is applied to IC's adult relatives with TC > 250 mg/dL and for children aged ≥3 years with TC > 220 mg/d; (3) all patients with hypercholesterolemia (HC) or FH receive appropriate lipid-lowering therapy; (4) all coronary events (CEs) occur in the half-time horizon of the model; (5) the diagnostic intervention applies only to the first year; (6) the cost of managing FH applies across the 10 year time horizon; and (7) the cost of CE consequences applies to the period between the event and the end of the time horizon (up to 10 years). CE was defined as the presence of any of the following: (1) myocardial infarction, proved by at least 2 of the following: classic symptoms, specific electrocardiographic changes, and increased levels of cardiac biomarkers; (2) angina pectoris, diagnosed as classic symptoms in combination with at least one unequivocal result of 1 of the following: exercise test, nuclear scintigram, dobutamine stress ultrasound scan or >70% stenosis on a coronary angiogram; (3) percutaneous coronary intervention or other invasive coronary procedures as indicated by his/her treating physician; and (4) coronary artery bypass grafting. The model was developed using Microsoft Excel 2013 software.

The model structure reproduces the chain of events of applying the NPFH (intervention arm) or following usual clinical practice (nonintervention arm; Fig. 1). The population entering the model is 9000 FH patients: 2250 IC and 6750 relatives, assuming the 1/3 ratio observed in the SAFEHEART registry.[9,10] The model calculates the costs and consequences that would occur if these FH 9000 subjects were treated as FH (intervention) compared to be treated as HC (no intervention). CE and cardiac deaths were considered as clinical consequences. Cerebrovascular events were not considered.

According to the NPFH, those subjects (≥18 years) with TC > 300 mg/dL detected in PC are checked with the Dutch Lipid Clinic Network diagnostic criteria (DLCNDC).[1,3,9] In case of a positive result (score ≥6),[3] the genetic test (GT) for FH is applied according to the NPFH protocol.[12,13] The GT positive result identifies the subject as suffering from FH, is classified as IC and treated as FH. IC adult relatives with TC > 250 mg/dL and children (<18 years) with TC > 220 mg/dL undergo GT. If positive, they are considered as FH patients and therefore begin to receive lipid-lowering therapy. The routine clinical practice arm reproduces what is done in the usual care setting without intervention.[14] In this arm, if at PC level, a subject with TC > 300 mg/dL is detected, the HC will be treated without any investigation of FH to the subject or his/her relatives.

In both decision tree arms, the outcomes variables (eg, CE, death) and the cost variables (eg, GT, treatments, cost of handling a CE) were established. In the intervention arm, knowing the prevalence of FH at PC level, in patients with TC > 300 mg/dL and the sensitivity and specificity of DLCNDC, true positives (TPs), false positives (FPs), true negatives (TNs), and false negatives (FNs) ratios for detecting an IC were calculated. The GT is applied to patients tested positive (TP + false positive) with DLCNDC criteria. As the sensitivity and specificity of the GT is 100%,[7] depending on the result of DLCNDC, the proportion of subjects with FH identified and unidentified and the proportion of subjects without FH were calculated. Subjects with FH treated as FH (TP), subjects with FH treated as HC (FN), and HC subjects treated as HC (TN) will have different probabilities of developing a CE in the next 10 years. HF confers a higher ASCVD risk than predicted by LDL-C level (at least 2 times the risk



FH: Familial hypercholesterolemia
CE: coronary event
C: Cost
E: Effectiveness
U: utility

To simplify the model, some chance nodes (circles) are presented without branches. The branches of the full model, from each chance node without branches, have the same structure as the random node of the upper branch.

Figure 1 Decision tree structure (simplified) for the model.

compared with individuals without FH for the same LDL-C level).[15] In turn, if the subject suffers CE, a mortality risk was applied[4,16] (Fundación Hipercolesterolemia Familiar. Unpublished data based on the SAFEHEART registry; Table 1).

Once the IC is detected, first-degree relatives are assessed, and depending on TC, GT is performed. Knowing the number of first-degree relatives for each IC, the proportion of adult relatives and the prevalence of FH in first-degree relatives, the number of relatives with FH, was calculated. These relatives also have risk of CE and death in the next 10 years (Table 1). In the nonintervention arm, the model assumes that in PC, patients with TC > 300 mg/dL are treated as HC and not investigated for FH. Knowing the prevalence of FH in patients with TC > 300 mg/dL, the proportion of subjects with FH was calculated (Table 1). As relatives with FH are treated as HC, they will have a greater risk of CE than relatives with FH treated as FH (Table 1). The probabilities and their sources used in the model are shown in Table 1.

Outcomes variables calculation: Effectiveness, utility

Two effectiveness measures were considered: CE and deaths avoided. These variables were calculated using the probability of CE and death in the intervention or the comparator arm. The incremental effectiveness of the intervention was calculated as the difference between the values for the intervention arm and the no intervention arm. The utility was estimated as the gain in quality-adjusted life years (QALYs) calculated as the difference between QALYs produced in the intervention arm and in

Table 1 Key variables for prevalence of hypercholesterolemia, diagnostic tests, risk of cardiac event, and quality of life used in the model scenarios

Variables	Scenario			Source
	Base case	Most favourable	Least favourable	
Prevalence				
Prevalence of HC in adults (TC > 300 mg/dL)	0.50%	0.45%	0.55%	SC[14]
Prevalence of FH in adults	0.33%	0.40%	0.29%	SC[1]
Prevalence of FH in adults with HC	66.67%	88.89%	51.95%	Calculated
Prevalence of FH in IC relatives with HC	95%	95%	95%	SC
Children proportion among the tested relatives	30.00%	25.00%	35.00%	SC
Diagnostic tests results				
Sensitivity of DLCNDC for FH	88.70%	91.30%	85.40%	[13]
Specificity of DLCNDC for FH	62.00%	66.80%	56.90%	[13]
Sensitivity of the genetic test	100%	100%	100%	[7]
Specificity of the genetic test	100%	100%	100%	[7]
Risk in IC (adults with TC > 300 mg/dL)				
Probability of CE in 10 y in FH treated as FH	14.09%	11.71%	16.75%	FHF*
Probability of CE in 10 y in FH treated as HC	26.09%	28.75%	23.71%	SC (+12%)
Probability of death if CE	23.08%	32.44%	15.81%	FHF*
Risk in IC adult relatives (TC > 250 mg/dL)				
Probability of CE in 10 y in FH treated as FH	10.51%	9.19%	11.94%	FHF*
Probability of CE in 10 y in FH treated as HC	22.51%	23.94%	21.19%	SC (+12%)
Probability of death if CE	24.80%	31.56%	19.39%	FHF*
Risk in IC children relatives (TC > 250 mg/dL)				
Probability of CE in 10 y in FH treated as FH	0.00%	0.00%	0.00%	SC
Probability of CE in 10 y in FH treated as HC	0.50%	1.00%	0.00%	SC
Probability of death if CE	5.00%	7.00%	1.00%	SC
QoL in adults				
QoL in the general population (adults)†	0.775	0.775	0.775	[17]
QoL deterioration because of CE (%)	12.08	13.84	10.22	[18]
QoL in an adult post CE†	0.682	0.668	0.696	Calculated
QoL in children				
QoL in the general population (children)†	0.879	0.879	0.879	[17]
QoL deterioration because of CE (%)	50.00	55.00	45.00	SC
QoL in a child post CE†	0.439	0.395	0.483	Calculated

CE, cardiac event; DLCNDC, Dutch Lipid Clinic Network diagnostic criteria; FH, familial hypercholesterolemia; HC, hypercholesterolemia; IC, index case; QoL, quality of life; SC, scientific committee; TC, total cholesterol.

*FHF: Fundación Hipercolesterolemia Familiar. Safeheart Registry follow-up (January 22, 2016). Unpublished data.

†Scale 0-1 (EuroQoL-5D).

the nonintervention arm. To calculate QALYs, the quality of life (QoL) of the Spanish general population was used, as measured by the EQ-5D, according to the latest National Health Survey.[17] A reduction in QoL was assigned for the CE to adults[18] and children (Table 1). When a patient dies, his/her QoL is assumed to be 0.

Direct costs calculations

FH diagnostic screening costs

The GT cost is €250 for IC and €110 for relatives using next-generation sequencing methods (data source: Gendiag.exe SL). The number of IC and relatives that undergo the GT was calculated using the prevalence of HC and FH in the general population, the prevalence of FH in patients with HC, and the sensitivity and specificity of DLCNDC (Table 1).

Medication costs

Lipid-lowering drugs (atorvastatin, rosuvastatin, simvastatin, and ezetimibe) and drugs for the management of a post-CE (aspirin, clopidogrel, enalapril, atenolol, bisoprolol, and diltiazem) were considered as medications. If more than 1 presentation, the cheapest price was used. The cost assigned to these drugs was the 2016 retail price plus value-added tax.[19] Drugs, dosages, and combinations applied were agreed by the SC.

Cardiac event management costs

The pattern of outpatient resource utilization at PC level was decided by the SC. The amount of hospital resources allocated in the model for the CE who dies and survives was calculated according to the Diagnosis-Related Group price[20] and their frequency in this type of patients in a cardiology service (Unpublished data. Hospital Universitario de Santiago de Compostela. Spain. Year 2013).

Total direct costs

The medication and CE management costs (and the GT for the intervention arm) constitute the direct costs. To calculate the total direct costs, annual cost for each type of event was assigned to the correspondent patient and year in each branch of the tree.

Indirect costs calculations

The costs of lost productivity because of post-CE or death were considered as indirect costs. To do this, the number of subjects to which each event applies was corrected by the ratio of working population[17] respect to the population of working age, assuming that unemployed subjects do not generate labor costs in case of illness. To calculate the number of days of sick leave for temporary disability for each event, official sources and scientific publications were used. The (official) theoretical number of days of sick leave because of acute myocardial infarction is 90 days of the year when suffering the heart attack and 30 days in the following years.[21] However, studies published in Spain estimate that the duration of sick leave can range between 190 and 322 days.[22–25] The proportion of patients who do not return to work (permanent disability pass) ranges, according to different studies, between 16% and 43%.[22–26] Given this variability in the information, it was assumed that the proportion of patients with full incapacitation after a CE is the average (26.5%), and among the remaining patients, half have the theoretical sick leave time (90 days) and the other half are on leave 243 days in the year of the event and 60 days in subsequent years.

To estimate the labor cost of a day lost, 3 options were considered: the contribution of a worker to the gross domestic product, the annual labor cost per worker, and the average annual earnings per worker.[17] The lowest of these 3 values is the average annual earnings per worker (€22,698). Given the conservative approach of this study, this estimate was chosen, which corresponds to a loss of €62 for each day of sick leave.

Efficiency calculation

The model considers 2 effectiveness indicators: CE and deaths avoided. Therefore, 2 incremental cost-effectiveness ratios (ICERs) were calculated. These are the ratio of incremental cost (ie, cost of intervention minus the cost of nonintervention) and incremental effectiveness (either CE avoided or deaths avoided over the time horizon of the model). The incremental cost-utility ratio (ICUR) or the cost per QALY gained was calculated using the same approach, dividing the incremental cost by the incremental utility (number of QALYs gained with the intervention).

Managing uncertainty: Sensitivity analysis

To estimate the effect that underlying uncertainty in the variables used in the model may have on the results of effectiveness, utility, and cost, a deterministic sensitivity analysis was carried out by constructing 3 scenarios: base case, most favorable, and least favorable to the intervention. The inputs for the most favorable and least favorable scenario regarding the likelihood of suffering a CE or die an IC or a relative were the 95% confidence intervals of the SAFEHEART registry follow-up analysis.[9,10] The figures applied to other variables used in the sensitivity analysis are shown in Table 1.

For calculating the ICER in the base case scenario, the ratio of incremental costs-to-outcomes used the central estimate of each. For the most favorable scenario, the lowest estimate of cost and highest estimate of effectiveness were used. For the least favorable scenario, the highest estimate of cost and lowest estimate of effectiveness were used. The same process was used in the cost-utility analysis to produce a base case, most favorable and least favorable scenario for the cost per QALY gained.

In addition, one-way sensitivity analysis was undertaken with the variables shown in Table 1. The values of these variables were changed one at a time, while maintaining base-case values for all other variables.

Results

FH subjects identification: Diagnostic tests results

ICs identification

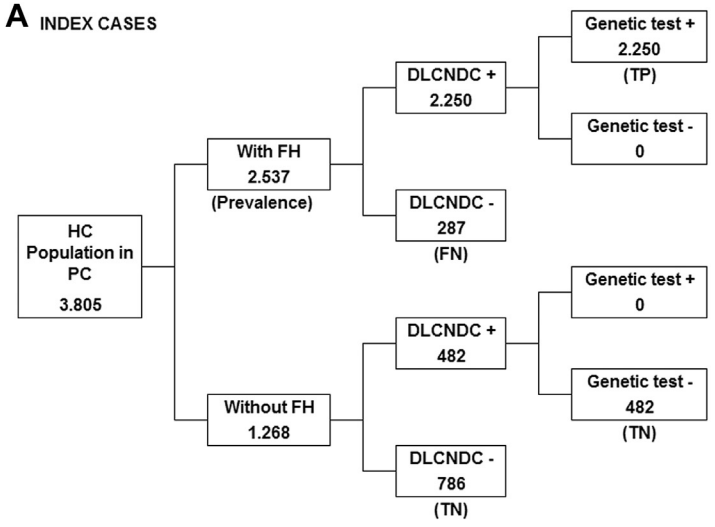
Based on the prevalence of HC, the prevalence of FH among HC patients, the sensitivity and specificity of DLCNDC and the GT in IC, 3805 subjects with TC > 300 md/dL will be required in PC to detect 2250 IC in the base case scenario. Using the DLCNDC, the PC physicians will identify 2732 patients who will require GT. In this process, 2250 patients will be TP (FH detected), 1268 will be TN (without FH and will be diagnosed as having no FH) and 287 will be FN (they have FH, but are diagnosed as not having FH). The sequential flow applied to both diagnostic tests is shown in Figure 2A. The lipid-lowering therapy will be applied to 2250 subjects classified as IC by tests.

Relatives of ICs identification

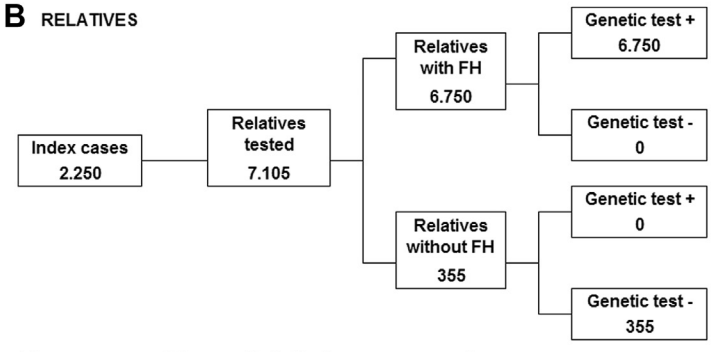
To detect 6750 cases of FH in relatives from the 2500 IC in the base case scenario, 7105 GTs on the relatives will be necessary. Of these, 6750 will suffer FH (TP). The sequential flows of GT applied on IC relatives are shown in Figure 2B.

Effectiveness

In the base case scenario, there would be 813 CEs with the intervention over 10 years, compared with 1661 in the comparator. Therefore, in the cohort of 9000 patients identified in a year, the intervention is predicted to prevent 847 CE over the subsequent 10 years. Similarly, the intervention prevents 203 coronary deaths (Table 2). In the most favorable scenario, the intervention would prevent 1147 CE and 361 deaths (Table 3). In the worst scenario, the intervention would avoid 562 CE and 103 deaths (Table 4).



Index cases		Have HF		
		Yes	No	Total
FH detected	Yes	2.250	0	2.250
	No	287	1.268	1.555
	Total	2.537	1.268	3.805
DLCND tests performed in PC				3.805
Genetic tests performed in PC				2.732
Index cases according to the genetic test				2.250



Relatives		Have HF		
		Yes	No	Total
FH detected	Yes	6.750	0	6.750
	No	0	355	355
	Total	6.750	355	7.105
Genetic tests performed in relatives				7.105
Relatives with FH according to the genetic test				6.750

Figures represent the results in the base case scenario

HC: hypercholesterolemia; PC: Primary care; FH: Familial hypercholesterolemia; DLCNDC: Dutch Lipid Clinic Network diagnostic criteria; FN: False negative; TP: True positive; TN: True negative.

Figure 2 Diagnostic tests results in index cases and relatives.

Table 2 Base case scenario: Outcomes of the intervention

Outcome	Intervention	No intervention	Difference
Cardiac events	813	1661	847*
Coronary deaths	196	400	203†
QALYs	62,175	61,408	767‡

QALY, quality-adjusted life year.
*Cardiac events avoided.
†Coronary deaths avoided.
‡QALYs gained.

Table 4 Least favorable scenario: Outcomes of the intervention

Outcome	Intervention	No intervention	Difference
Cardiac events	901	1463	562*
Coronary deaths	161	265	103†
QALYs	62,589	62,191	398‡

QALY, quality-adjusted life year.
*Cardiac events avoided.
†Coronary deaths avoided.
‡QALYs gained.

Utility

The intervention would generate 62,175 QALYs in 10 years compared with 61,408 QALYs without the intervention. Therefore, the intervention arm will produce 767 QALYs more than the no intervention arm (Table 2). Similarly, the intervention generates an incremental gain of 1315 QALYs in the most favorable scenario (Table 3), and 398 QALYs the least favorable scenario (Table 4).

Costs

In the base case scenario, the sum of direct costs across the 9000 individuals (diagnosis + FH lipid-lowering therapy + event management) of the intervention amounts to €59.995 million. The nonintervention does not have diagnostic cost, the lipid-lowering treatment costs are lower than in the intervention, but the costs of managing more events outweigh the intervention. The incremental direct cost of intervention relative to nonintervention is €22.696 million (Table 5 and Fig 3). On the indirect costs, the intervention produces a saving of €25.518 million because of less sick leave days. Accordingly, as the saving in labor costs is greater than the increase in direct costs, a total saving is achieved in the social costs of €2.822 million (Table 5 and Fig 3).

In the most favorable scenario, the incremental direct cost is €20.764 million. Regarding the indirect costs, savings of €40.456 million occurs, so that the social perspective obtains a €19.691 million saving (Table 6). In the worst scenario, the incremental direct cost is €24.547 million, indirect costs decreased by €14.047 million, so that from the social perspective, cost increase in €10.500 million (Table 7).

Table 3 Most favorable scenario: Outcomes of the intervention

Outcome	Intervention	No intervention	Difference
Cardiac events	729	1876	1,147*
Coronary deaths	232	594	361†
QALYs	61,765	60,450	1,315‡

QALY, quality-adjusted life year.
*Cardiac events avoided.
†Coronary deaths avoided.
‡QALYs gained.

Efficiency

Cost–effectiveness

In the base case scenario, from the payer (NHS) perspective, the ICER is €26,792 per CE avoided and €111,567 per avoided death. With the social perspective, the intervention is dominant relative to the comparator (ie, the effectiveness increases and the costs decreases; Table 8).

In the most favorable scenario, with the NHS perspective, the ICERs are €18,103 per CE avoided and €57,484 per death avoided, whereas from the social perspective, the ICERs are dominant (Table 9). In the worst scenario, with NHS perspective, the ICERs are €43,643 per CE avoided and €237,275 per death avoided. With the social perspective, the ICERs are €18,668 per CE avoided and €101,493 per avoided death (Table 10).

Cost/utility

With the NHS perspective, the ICUR is €29,608 per QALY gained, whereas with the social perspective, the

Table 5 Base case scenario: Costs (euros) of the intervention

Direct costs	Intervention	No intervention	Difference
Diagnostic	1,464,569	0	1,464,569
HC treatment	50,042,753	19,963,512	30,079,241
Cardiac events management	8,487,825	17,335,567	−8,847,742
Total	**59,995,147**	**37,299,078**	**22,696,068**
Indirect costs	24,531,615	50,049,627	−25,518,012
Total costs (societal)	**84,526,762**	**87,348,705**	**−2,821,943**

HC, hypercholesterolemia.
Total values are indicated in bold.

Table 6 Most favorable scenario: Costs (euros) of the intervention

Direct costs	Intervention	No intervention	Difference
Diagnostic	1,369,647	0	1,369,647
HC treatment	51,537,333	20,100,017	31,437,315
Cardiac events management	7,644,338	19,687,059	−12,042,720
Total	**60,551,318**	**39,787,076**	**20,764,242**
Indirect costs	25,782,718	66,238,452	−40,455,734
Total costs (societal)	**86,334,036**	**106,025,528**	**−19,691,492**

HC, hypercholesterolemia.
Total values are indicated in bold.

Table 8 Base case scenario: Efficiency of the intervention

Outcome	Cost (€) per outcome unit obtained	
	Only direct costs (payer perspective)	Direct and indirect costs (social perspective)
Cardiac event avoided	26,792	−3331
Coronary deaths avoided	111,567	−13,872
QALYs gained	29,608	−3681

QALY, quality-adjusted life year.

intervention is dominant (Table 8 and Fig 3). In the most favorable scenario, with the NHS perspective, the ICUR is €15,786 per QALY gained, and with the social perspective, the intervention is dominant (Table 9 and Fig 3). In the worst scenario, with NHS perspective, the ICUR is €61,696 per QALY gained, whereas from the social perspective is €26,390 per QALY gained (Table 10 and Fig 3).

The results of one-way sensitivity analyses (Table 11) show that from the social perspective, the NPFH is dominant (cost saving) in all the 28 built scenarios. From the NHS perspective, the ICUR was below the threshold of €30,000/QALY in 20 of the 28 scenarios. The ICUR is mainly sensitive to the uncertainty because of the probability of CE in 10 years, the probability of death if CE, and the QoL in adults post CE.

Discussion

This study shows that a standardized implementation of a national cascade screening program for FH, using GT supplemented with the measurement TC and appropriate treatment is a cost-effective strategy for preventing CAD in families with FH. Our results show that in the base case scenario, the NPFH applied for 1 year avoids 847 CE and 203 deaths during a 10-year follow-up period. At the same time, the NPFH gains 767 QALYs at a cost of €29,608/QALY with the payer perspective, which is below the €30,000/QALY considered as the ethically acceptable threshold to be funded with public money in Europe. Considering the social perspective, the NPFH is dominant that is, saves lives, avoids CAD, and gains QALYs producing net money savings for society. Thus, it is very reasonable to consider that the implementation of the NPFH is a very efficient strategy from the NHS perspective, and especially from the social perspective.

Our findings are consistent with 1 study performed in Australia considering only direct costs, showing an ICER per QALY gained, through a cascade screening based on GT, ranging from dominant to 16,880 Australian dollars according to the one-way sensitivity analysis and from 2004 to 5228 Australian dollars according to the 95% confidence intervals in the probabilistic sensitivity analysis.[7]

The clinical effectiveness of genetic testing has been demonstrated previously.[5–7] Advances in next-generation sequencing have reduced costs.[21] Therefore, the major cost driver for cascade testing is not GT but treatment over the remaining lifetime. However, with potent statins now off-patent, the overall cost has been also reduced considerably.

In the plan presented in this study, most FH patients would be managed at the PC level. GPs would be able to refer patients to specialists if they need advice about management, especially with the new treatment with PCSK9 inhibitors in high-risk FH patients. This model of care has shown a cost reduction when compared with the cost of the estimates undertaken by National Institute for Health and Care Excellence.[27]

In any event, the advent of the expensive PCSK9 inhibitors would influence, to some extent, the cost-to-effectiveness ratios of the cascade screening. All health economic analyses using these agents need to take account

Table 7 Least favorable scenario: Costs (euros) of the intervention

Direct costs	Intervention	No intervention	Difference
Diagnostic	1,606,672	0	1,606,672
HC treatment	48,545,226	19,758,937	28,786,289
cardiac events management	9,359,773	15,206,218	−5,846,445
Total	**59,511,671**	**34,965,155**	**24,546,516**
Indirect costs	22,330,831	36,377,672	−14,046,841
Total costs (societal)	**81,842,502**	**71,342,826**	**10,499,675**

HC, hypercholesterolemia.
Total values are indicated in bold.

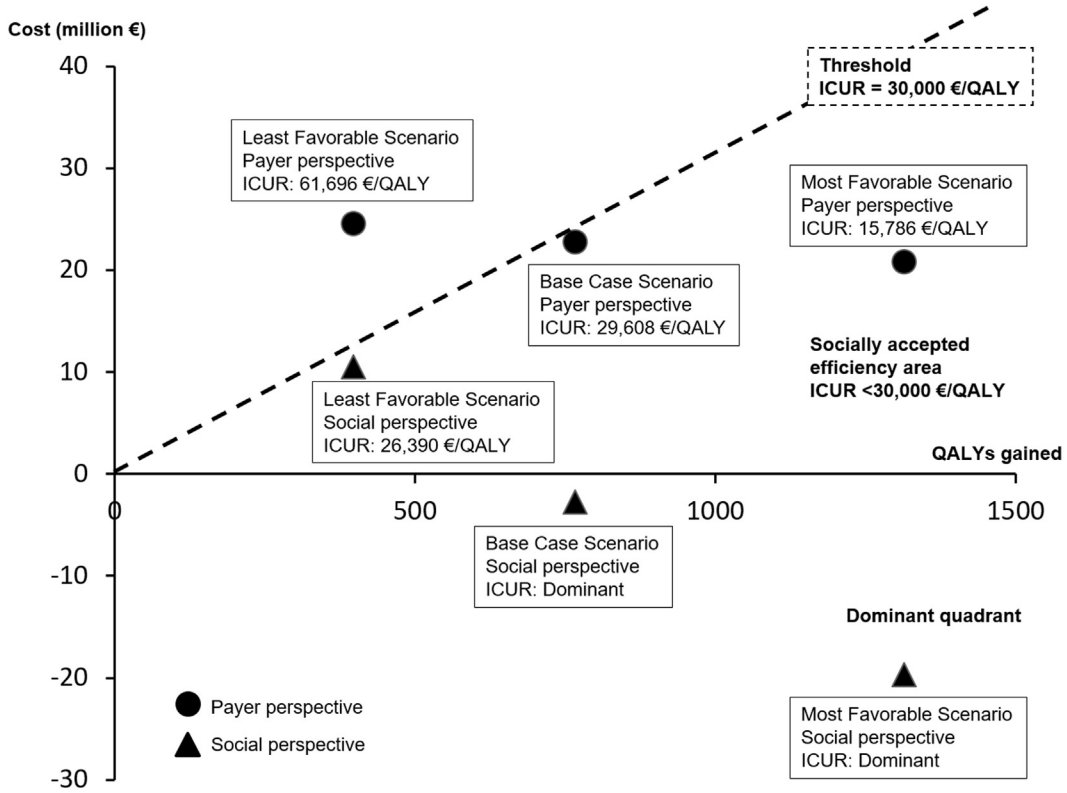


Figure 3 Incremental cost-utility ratio (cost per QALY gained) of the NPFH implementation considering the payer and social perspectives: sensitivity analysis.

of the unmet medical needs of higher risk patients with FH, the broader impact of therapy on first and recurrent cardiovascular events, the falling costs of drug therapy over time and the societal benefits of effective interventions.[28] Analyses based on broader populations, assumptions on limited effect size of the intervention, and restricted focus of first cardiovascular events are likely to lead to misleading conclusions.[28,29] A more robust evaluation of the cost-effectiveness of these new agents will depend on the outcome of ongoing clinical endpoint trials,[28] although one must concede that these studies are not being undertaken exclusively in patients with FH. By now, it could be reasonable to assume that the cost-effectiveness of using PCSK9 inhibitors in FH is supported on their restricted use in higher risk patients, according to 2 analyses from National Institute for Health and Care Excellence.[30,31]

The model applied in our analysis uses the best available scientific evidence, including real and robust data obtained from the screening program of the SAFEHEART registry.[9,10] Furthermore, the model considers adults and children, and a sensitivity analysis was performed for managing the underlying uncertainty. Nevertheless, we acknowledge some limitations. Although the best evidence has been used, there are many areas with scarce evidence. The time horizon is 10 years, rather than the cohort life expectancy period, but

Table 9 Most favorable scenario: Efficiency of the intervention

Outcome	Cost (€) per outcome unit obtained	
	Only direct costs (Payer perspective)	Direct and indirect costs (Social perspective)
Cardiac event avoided	18,103	−17,168
Coronary deaths avoided	57,484	−54,514
QALYs gained	15,786	−14,971

QALY, quality-adjusted life year.

Table 10 Least favorable scenario: Efficiency of the intervention

Outcome	Cost (€) per outcome unit obtained	
	Only direct costs (Payer perspective)	Direct and indirect costs (Social perspective)
Cardiac event avoided	43,643	18,668
Coronary deaths avoided	237,275	101,494
QALYs gained	61,696	26,390

QALY, quality-adjusted life year.

Table 11 Impact of key variables on incremental cost-utility ratios, using one-way sensitivity analyses

Variable	Value	Incremental cost/QALY (€)	
		NHS perspective	Social perspective
Prevalence of FH in adults with HC (TC > 300 mg/dL)	88.89%	29,490	Dominant
Prevalence of FH in adults with HC (TC > 300 mg/dL)	51.95%	29,742	Dominant
Children proportion among the tested relatives	25.00%	29,339	Dominant
Children proportion among the tested relatives	35.00%	29,904	Dominant
Sensitivity of DLCNDC for FH	91.30%	29,604	Dominant
Sensitivity of DLCNDC for FH	85.40%	29,614	Dominant
Specificity of DLCNDC for FH	66.80%	29,589	Dominant
Specificity of DLCNDC for FH	56.90%	29,629	Dominant
Risk in IC (adults with TC > 300 mg/dL)			
Probability of CE in 10 y in FH treated as FH	11.71%	27,276	Dominant
Probability of CE in 10 y in FH treated as FH	16.75%	32,580	Dominant
Probability of CE in 10 y in FH treated as HC	28.75%	26,982	Dominant
Probability of CE in 10 y in FH treated as HC	23.71%	32,275	Dominant
Probability of death if CE	32.44%	26,932	Dominant
Probability of death if CE	15.81%	32,073	Dominant
Risk in IC adult relatives (TC > 250 mg/dL)			
Probability of CE in 10 y in FH treated as FH	9.19%	26,822	Dominant
Probability of CE in 10 y in FH treated as FH	11.94%	33,160	Dominant
Probability of CE in 10 y in FH treated as HC	23.94%	26,552	Dominant
Probability of CE in 10 y in FH treated as HC	21.19%	32,886	Dominant
Probability of death if CE	31.56%	25,753	Dominant
Probability of death if CE	19.39%	33,621	Dominant
Risk in IC children relatives (TC > 250 mg/dL)			
Probability of CE in 10 y in FH treated as HC	0.00%	30,162	Dominant
Probability of CE in 10 y in FH treated as HC	1.00%	26,690	Dominant
Probability of death if CE	1.00%	29,650	Dominant
Probability of death if CE	7.00%	29,588	Dominant
QoL in adults post CE*	0.668	28,947	Dominant
QoL in adults post CE*	0.696	30,338	Dominant
QoL in children post CE*	0.483	29,641	Dominant
QoL in children post CE*	0.395	29,575	Dominant

CE, cardiac event; DLCNDC, Dutch Lipid Clinic Network diagnostic criteria; FH, familial hypercholesterolemia; HC, hypercholesterolemia; IC, index case; QALY, quality-adjusted life year; NHS, National Health System; QoL, quality of life; TC, total cholesterol.

*Scale 0-1 (EuroQoL-5D).

extrapolating data for more than 10 years would be risky because of uncertainty and the lack of information. A 10-year time horizon is short for most patients whose mean age at the time of screening, as shown in the SAFEHEART registry, is 46 years. Extending the timeframe of FH model to 30 years would lead to even greater estimates of cost-effectiveness. We think that the analysis performed illustrates quite well the cost and outcomes derived for 10 years of follow-up for every cohort annually screened. Finally, stroke and peripheral artery disease have not been considered. If these events would have been considered, the NPFH efficiency would be much greater.

Practical implications

The lack of diagnosis creates a barrier for the effective prevention of premature ASCVD and impacts the QoL and economic and social burden of individuals and families with FH. The early detection and treatment of FH patients is a public health challenge for the Health Systems and represents an unmet medical need for patients. To improve the care of these patients, PC physicians should be trained in the diagnosis and treatment of FH. The results obtained in this study provide support for the implementation of the NPFH that may close the gap in the lack of detection and treatment and will contribute to improve the FH care and to save lives at a socially acceptable cost. It is reasonable to think that the findings of this study could be extrapolated to other European countries with similar developed healthcare systems in which the implementation of the FH detection strategy would be also cost-effective.

Conclusions

The implementation of an NPFH using GT and appropriate lipid treatment is a cost-effective strategy for preventing CE. In the base case scenario, the NPFH applied

1 year avoids a relevant number of CE events and deaths during a 10 year follow-up and the cost per QALY gained is within the ethically acceptable limits to be funded with public money. Furthermore, considering the social perspective, the NPFH is dominant, implying important health gain and money savings for the society. Implementation of such a strategy is likely to be also cost-effective in other European countries with similar developed healthcare systems.

Acknowledgment

Authors' contributions: All the authors listed in the article contributed significantly to this work, and all of them meet the full criteria and requirements for authorship. All the authors contributed to conception and design of the study, analysis and interpretation of data, revising the article and all of them approve the article submitted.

Clinical trial registration: ClinicalTrials.gov number NCT02693548.

This work was supported by the Instituto de Salud Carlos III (grant number G03/181); Fondo de Investigación Sanitaria (grant number FIS PI12/01289); and Centro Nacional de Investigacion Cardiovascular (grant number 08-2008).

Conflicts of interest: none.

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