Online supplementary file 5: Cost-effectiveness of alternative cascade protocols

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Model implementation

We built the model as a series of four linked modules, starting in the last stage of the cascade (Stage 3: Testing relatives) and moving backwards to Stage 2: Contacting relatives, Stage 1: Testing relatives, and finally the fourth module connecting Stage 2 to Stage 1 to produce results by index family.

Stage 1: Index selection

This module uses a decision tree to calculate the proportion of indexes selected to the cascade, by their true FH status and by whether the genetic test was conducted, given the selection strategy, clinical score and clinical score cut-off (Figure 1).

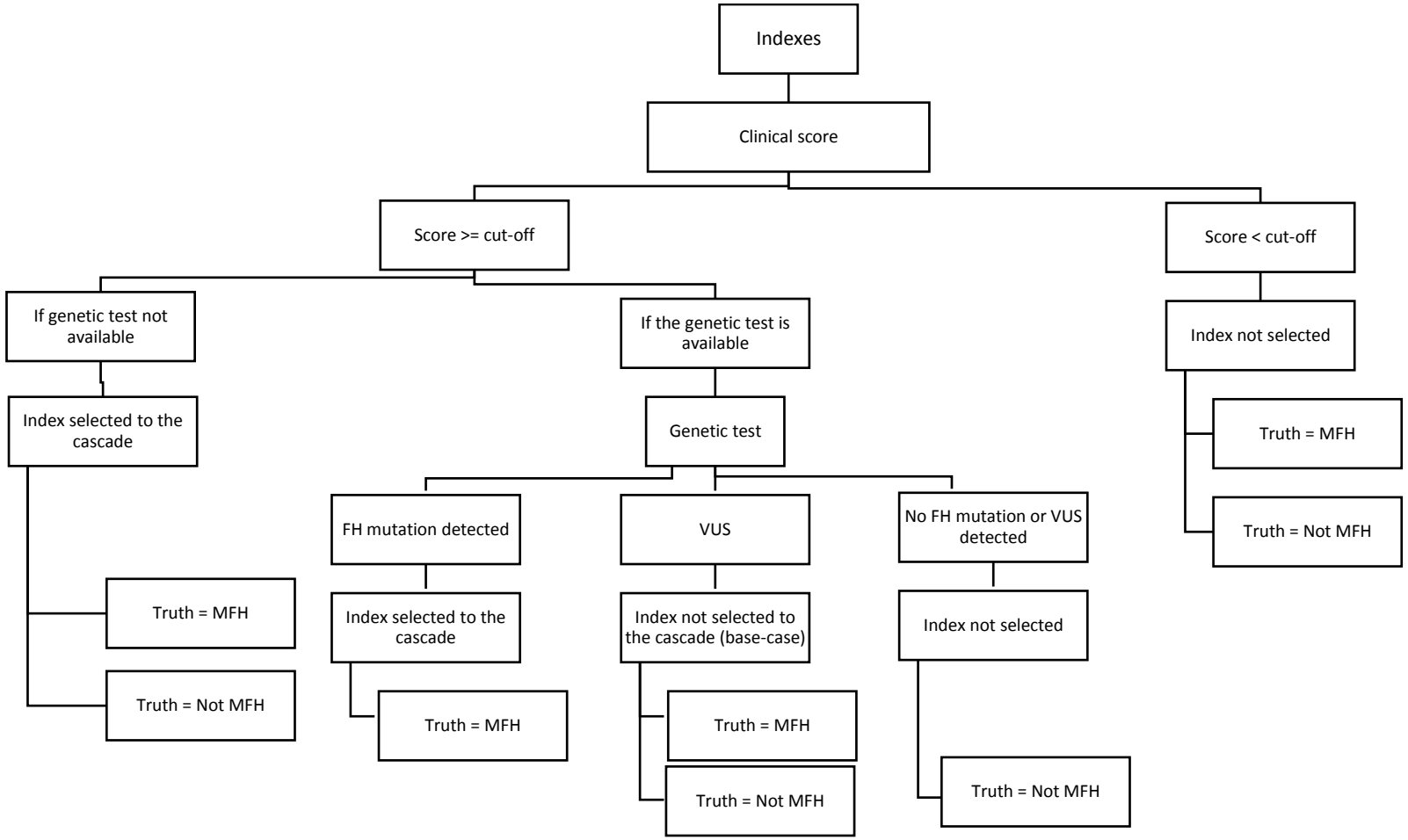


Figure 1: Decision tree of strategies to select indexes to the cascade

Abbreviations: FH: Familial Hypercholesterolaemia, MFH: Monogenic Familial Hypercholesterolaemia; PT-LDLC: Pre-Treatment Low-Density Lipoprotein Cholesterol.

Stage 2: Contacting relatives

This module calculates the probability that relatives are tested given their age and sex, for both methods of contact (direct and indirect) and their kinship degree to the index (1st or 2nd degree), using the logistic model estimated in the analysis of PASS data. It takes the results of the module on strategies to test relatives (stage 3) and adjusts them by the probability that relatives are tested, with relatives who are not tested having the outcomes of relatives who are not diagnosed. Given the age and sex distribution of contacted relatives, the model calculates the outcomes of relatives by FH status, the set of testing strategies, method of contact and kinship degree to the index.

Subsequently, the module calculates the outcomes per index family selected for cascade testing, depending on their FH status of the index, the type of cascade (sequential or concomitant), the method of contact and the set of testing strategies, using decision trees depending on the pattern of contact and FH status of the index (Figures 2-4).

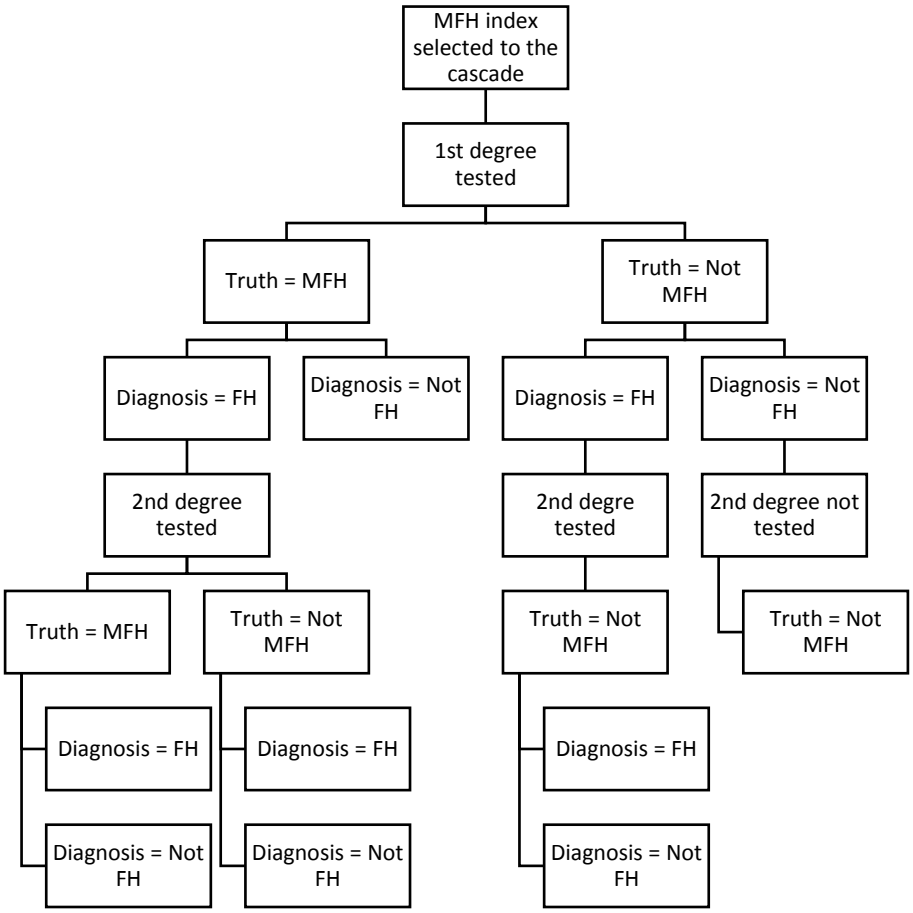


Figure 2: Decision tree for sequential cascade if the FH index is selected to the cascade

Abbreviations: FH: Familial Hypercholesterolaemia, FH: Monogenic Familial Hypercholesterolaemia; PT-LDLC: Pre-Treatment Low-Density Lipoprotein Cholesterol.

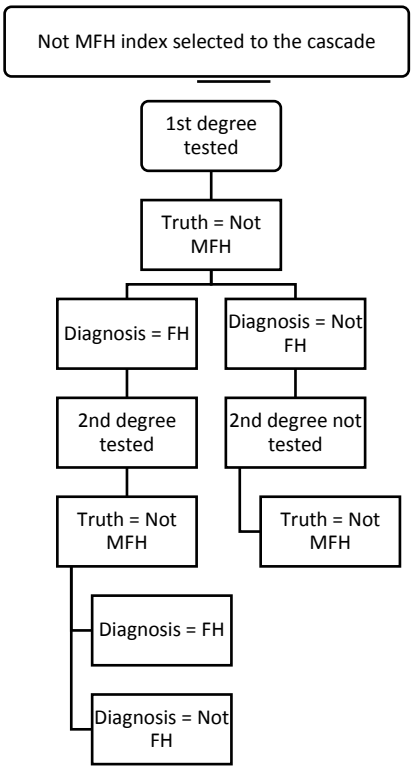


Figure 3: Decision tree for sequential cascade if the Not FH index is selected to the cascade

Abbreviations: FH: Familial Hypercholesterolaemia, MFH: Monogenic Familial Hypercholesterolaemia; PT-LDLC: Pre-Treatment Low-Density Lipoprotein Cholesterol.

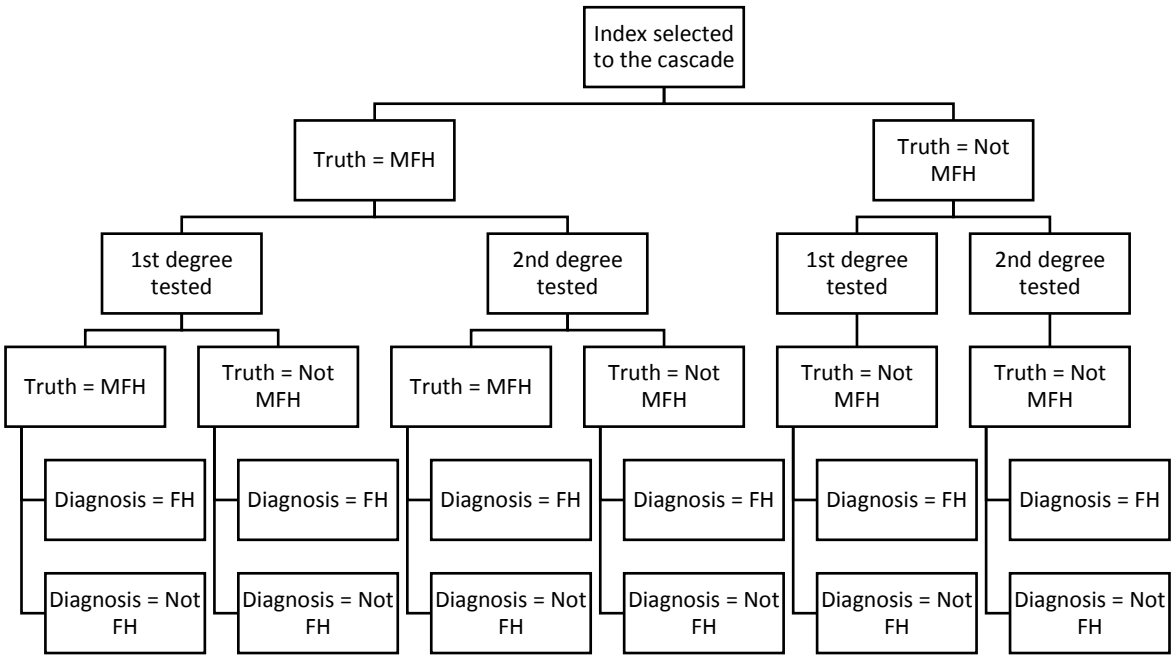


Figure 4: Decision tree for concomitant cascade

Abbreviations: FH: Familial Hypercholesterolaemia, MFH: Monogenic Familial Hypercholesterolaemia; PT-LDLC: Pre-Treatment Low-Density Lipoprotein Cholesterol.

Stage 3: Testing relatives

This module is formed by decision trees on each testing strategy (Figures 5-9). The population of relatives enters the model as subgroups according to their monogenic familial hypercholesterolaemia (FH) status, age, sex, cardiovascular (CV) history and lipid lowering treatment (LLT) at the time of the cascade. The model calculates the outcomes of each subgroup given the testing strategy, and then calculates their weighted average by group defined by FH status, age and sex, and given the testing strategy, weighted by the proportion of relatives with prior CV history, on LLT and by their pre-treatment low density lipoprotein cholesterol (LDLC). The long-term health outcomes and costs depending on whether relatives were treated for FH are inputs to this decision tree. The output of module 3 is a table with the outcomes of relatives given their FH status, age, sex, and the testing strategy.

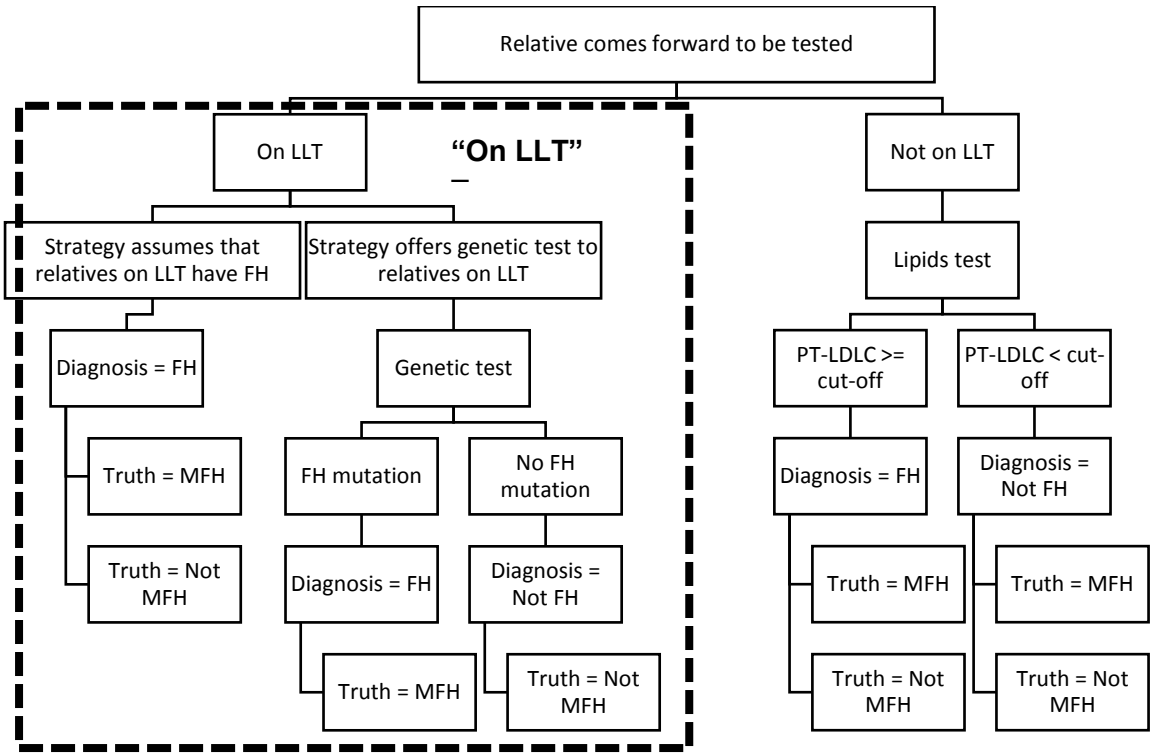


Figure 5: Decision tree for strategies "N1"

Abbreviations: FH: Familial Hypercholesterolaemia, MFH: Monogenic Familial Hypercholesterolaemia; PT-LDLC: Pre-Treatment Low-Density Lipoprotein Cholesterol.

The box delimited by the dashed rectangle indicates the decision tree for the strategies if relatives are on LLT at the time of the cascade, which is the same for all testing strategies.

In these and following diagrams, the term "diagnosis" represents the observed result of the testing strategy, which determines the management of relatives (as familial hypercholesterolaemia (FH) patient or not). The term "truth" refers to the true disease status of relatives, which is either having FH or not.

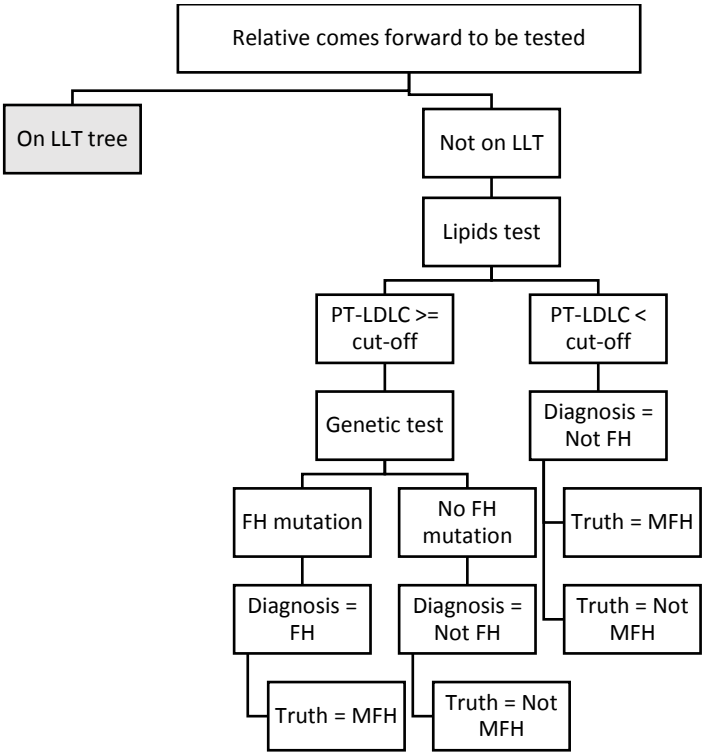


Figure 6: Decision tree for strategy "N2"

Abbreviations: FH: Familial Hypercholesterolaemia, MFH: Monogenic Familial Hypercholesterolaemia; PT-LDLC: Pre-Treatment Low-Density Lipoprotein Cholesterol.

See Figure 1: Decision tree for strategy "N1" for "On LLT Tree".

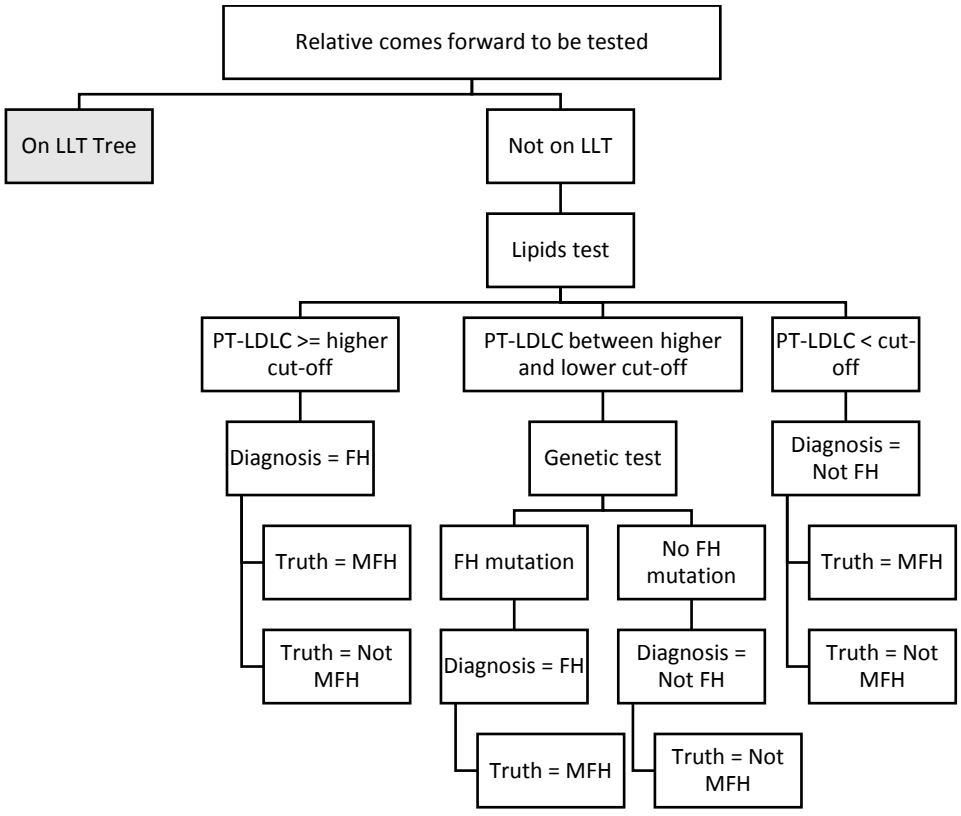


Figure 7: Decision tree for strategy "N3"

Abbreviations: FH: Familial Hypercholesterolaemia, MFH: Monogenic Familial Hypercholesterolaemia; PT-LDLC: Pre-Treatment Low-Density Lipoprotein Cholesterol.

See Figure 1: Decision tree for strategy “N1” for “On LLT Tree”.

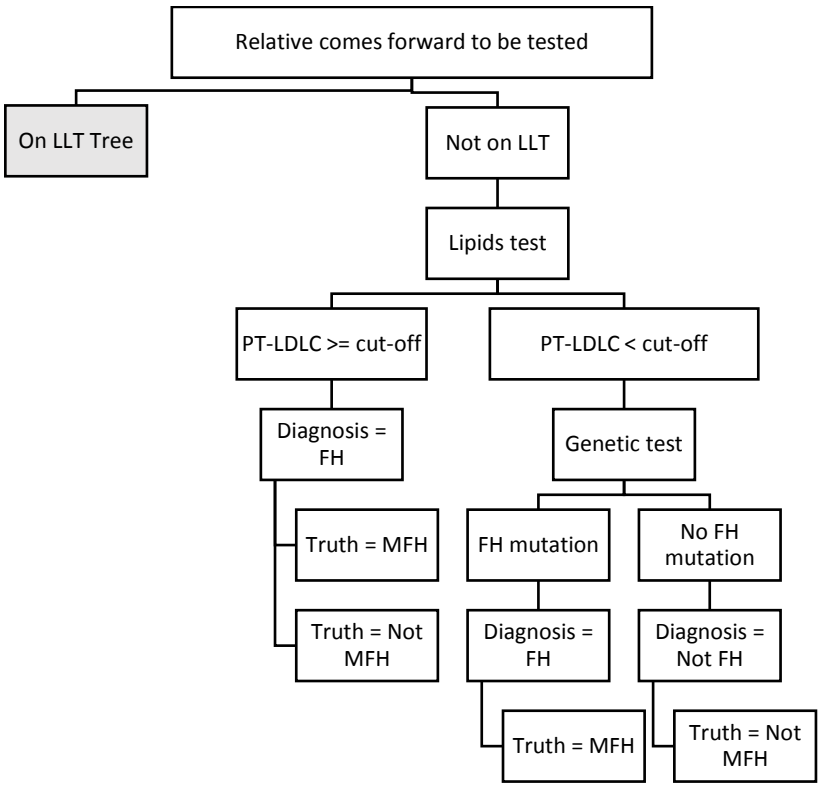


Figure 8: Decision tree for strategies "N4"

Abbreviations: FH: Familial Hypercholesterolaemia, MFH: Monogenic Familial Hypercholesterolaemia; PT-LDLC: Pre-Treatment Low-Density Lipoprotein Cholesterol.

See Figure 1: Decision tree for strategy “N1” for “On LLT Tree”.

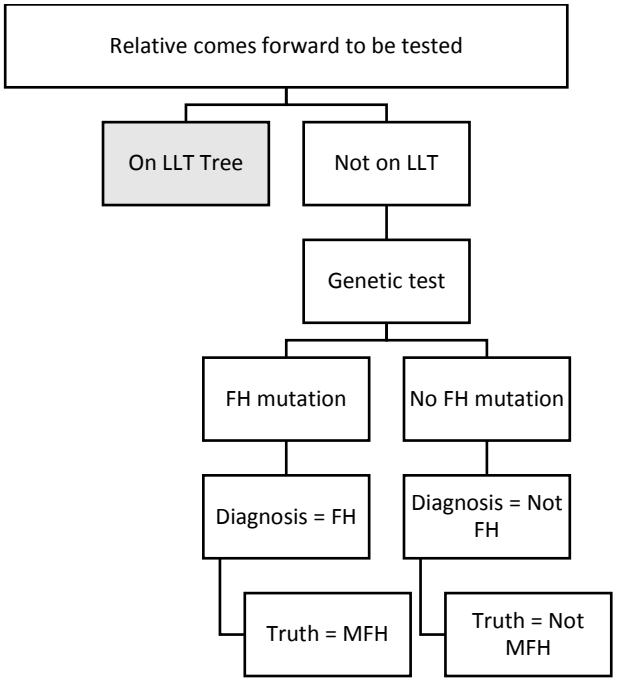


Figure 9: Decision tree for strategies "N5"

Abbreviations: FH: Familial Hypercholesterolaemia, MFH: Monogenic Familial Hypercholesterolaemia; PT-LDLC: Pre-Treatment Low-Density Lipoprotein Cholesterol.

See Figure 1: Decision tree for strategy "N1" for "On LLT Tree".

Module linking indexes to relatives

This module uses the results of the module on the strategies to ensure relatives are tested and of the module on strategies to select indexes to the cascade, to calculate the outcomes per index family assessed to the cascade (Figure 10).

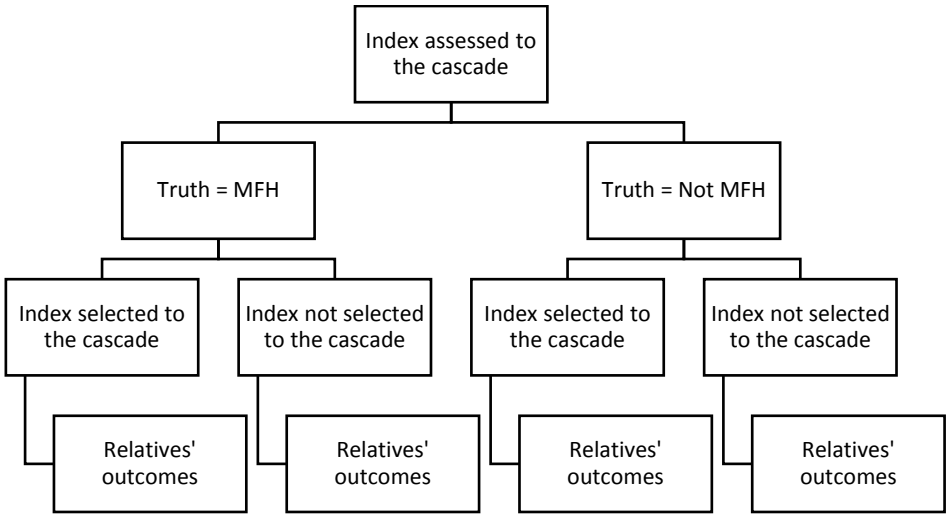


Figure 10: Decision tree linking indexes to relatives

Abbreviations: FH: Familial Hypercholesterolaemia, MFH: Monogenic Familial Hypercholesterolaemia; PT-LDLC: Pre-Treatment Low-Density Lipoprotein Cholesterol.

Model inputs

Clinical cascade data

Table 1: Model Inputs for module 1 – selection of indexes to the cascade

Parameter	Percentage	numerator	Denominator	Distribution	Source
Clinical inputs common to all clinical scores					
Indexes who have a VUS (not reclassified into pathogenic or not at the time of the selection to the cascade)	4%	114	2867	Beta	PASS Wales and Wessex
Indexes with VUS who were reclassified to FH out of those who were reclassified	75%	88	118	Beta	
Probability that indexes have FH given their WDLCN category – Dutch data; Base-case					
WDLCN = 6	15%	96	661	Dirichlet	PASS Wales
WDLCN = 7	16%	51	318		
WDLCN = 8	14%	32	222		
WDLCN = 9	26%	58	221		
WDLCN = 10	30%	60	197		
WDLCN = 11	29%	24	83		
WDLCN >=12	64%	184	286		
Probability that indexes have FH given their Simon Broome categories – Wessex data; Scenario					
Simon Broome possible FH	29%	249	853	Gamma	PASS Wessex
Simon Broome definite FH	58%	15	26		
Probability that indexes have FH given their AWDLCN categories – Welsh data; Scenario					
AWDLCN = 6	26%	35	134	Gamma	PASS

Parameter	Percentage	numerator	Denominator	Distribution	Source
AWDLCN = 7	20%	26	127		Wales
AWDLCN = 8	32%	33	104		
AWDLCN = 9	34%	42	122		
AWDLCN = 10	48%	30	63		
AWDLCN = 11	33%	18	54		
AWDLCN >=12	73%	122	168		

AWDLCN: Age-adjusted Welsh modified Dutch Lipid Clinic Network FH: Familial hypercholesterolaemia; MFH: Monogenic FH; VUS: variance of unknown significance; WDLCN: Welsh modified Dutch Lipid Clinic Network.

Table 2: Relatives' characteristics

Parameter		Mean or %	n or SE	N	Distribution	Source
Proportion of females in those relatives who completed the cascade						
PASS Wales (Base-case)		57%	683	1205	Beta	PASS Wales
PASS Wessex (Scenario)		60%	301	501		PASS Wessex
Proportion of females in those relatives who were contacted						
PASS Wales (Base-case)		53%	1061	2019	Beta	PASS Wales
PASS Wessex (Scenario)		54%	539	1002		PASS Wessex
Age distribution in those who completed the cascade						
PASS Wales (Base-case)	0-9	5%	58	1205	Dirichlet	PASS Wales
	10-17	20%	237			
	18-39	35%	424			
	40-59	27%	327			
	60+	13%	159			
PASS Wessex (Scenario)	0-9	21%	105	501		PASS Wessex
	10-17	20%	98			
	18-39	24%	119			
	40-59	22%	112			
	60+	13%	67			
Age distribution in the relatives who were contacted for cascade testing						
PASS Wales (Base-case) Not available in PASS Wessex	0-9	9%	164	1811	Dirichlet	PASS Wales
	10-17	15%	280			
	18-39	35%	635			
	40-59	26%	463			
	60+	15%	269			
Prevalence of FH in relatives who are tested						
Base-case	1st degree of index with FH	50%	NA	NA	Fixed	Assumption given inheritance pattern
	2nd degree of index with FH	25%	NA	NA		
PASS Wales (Scenario)	1st degree of index with FH	60%	440	733	Beta	PASS Wales
	1st degree relative of 1st degree	48%	225	468		

Parameter		Mean or %	n or SE	N	Distribution	Source
	relative with FH **[1,2]**					
PASS Wessex (Scenario)	1st degree of index with FH	63%	205	325		PASS Wessex
	1st degree relative of 1st degree relative with FH **[1,2]**	48%	78	161		
Number of relatives						
PASS Wales (Base-case)	1st degree per index	2.20	0.09	NA	Gamma	PASS Wales
	2nd degree per 1st degree **[1]**	1.79	0.15	NA		
PASS Wessex (Scenario)	1st degree per index	2.23	0.11	NA		PASS Wessex
	2nd degree per 1st degree **[1]**	1.24	0.16	NA		
Probability that FH relatives have prior CV history at the time of the cascade, by age						
PASS Wales (Base-case)	0-9	0%	0	32	Beta	PASS Wales
	10-17	0%	0	110		
	18-39	2%	SN	SN		
	40-59	14%	19	138		
	60+	31%	17	55		
PASS Wessex (Scenario)	0-9	0%	SN	SN		PASS Wessex
	10-17	0%				
	18-39	0%				
	40-59	6%				
	60+	35%	9	26		
Probability that FH relatives are on LLT if they had prior CVD history, by age, at the time of cascade						
PASS Wales (Base-case)		86%	25	29	Beta	PASS Wales
PASS Wessex (Scenario)		100%	SN	SN		PASS Wessex
Probability that FH relatives are on LLT if no prior CVD history, by age, at the time of cascade						
PASS Wales (Scenario)	0-9	7%	SN	SN	Beta	PASS Wales
	10-17	15%	15	97		
	18-39	36%	66	182		
	40-59	62%	59	95		
	60+	86%	25	29		
PASS Wessex (Base-case)	0-9	0%	SN	SN		PASS Wessex
	10-17	0%				
	18-39	8%				
	40-59	27%				
	60+	50%				
Probability that Not FH relatives have prior CVD history, by age, at the time of the cascade						
All relatives who do not have FH	0-39	0%	NA	NA	None	Assumption
	40-59	11%	420	3846	Beta	HSE 2017 [1]
	60+ males	38%	921	2419		
	60+ females	27%	249	939		

Parameter		Mean or %	n or SE	N	Distribution	Source
Probability that Not FH relatives are on LLT if they had prior CVD history						
Relatives aged>= 40 years		81%	74113	91497	Beta	Steen et al 2017 [2]
Probability that Not FH relatives are on LLT if they did not have prior CV history, by age, at the time of the cascade						
All relatives who do not have FH	0-39	0%	NA	NA	None	Assumption
	40-59 males	9%	99	1084	Beta	HSE 2017 [1]
	40-59 males	6%	69	1106		
	60+ males	38%	121	319		
	60+ females	33%	144	431		
Proportion of out-of-area relatives						
PASS Wales (base-case)		24%	1992	2634	Beta	PASS Wales
PASS Wessex (scenario)		29%	1006	1414		PASS Wessex

AWDLCN: Age-adjusted Welsh modified Dutch Lipid Clinic Network; CVD: cardiovascular disease; FH: Familial hypercholesterolaemia; HSE: Health Survey for England; LLT: Lipid Lowering Therapy; FH: Monogenic FH; NA: Not applicable; SN: supressed due to being a number below 7; VUS: variance of unknown significance; WDLCN: Welsh modified Dutch Lipid Clinic Network.

[1] Obtained from the analysis of relatives who were 2nd degree or greater to the index, assumed generalisable to 2nd degree relatives.

[2] The model uses the probability that the 2nd degree relative to the index has monogenic familial hypercholesterolaemia, calculated as the probability that the 1st degree of the index times the probability of the 1st degree relative to the 1st degree of the index (e.g. 60% * 48% = 29%)

Table 3: Coefficients and Cholesky matrix for the probability of completing the cascade, according to data from PASS Wales

Parameter	Mean (log odds ratio)	Cholesky matrix						
		Sex; =1 if female	Degree; =1 if 1st degree	Method of contact; =1 if direct	Method of contact; =1 if other	Method of contact; relative aged <18 years	Method of contact; =1 if unknown	Constant
Sex; =1 if female	0.44	0.09	0.00	0.00	0.00	0.00	0.00	0.00
Degree; =1 if 1st degree	0.44	0.00	0.10	0.00	0.00	0.00	0.00	0.00
Method of contact; =1 if direct	0.75	0.00	0.00	0.12	0.00	0.00	0.00	0.00
Method of contact; =1 if other	1.26	0.00	0.01	0.07	0.14	0.00	0.00	0.00
Method of contact; relative aged <18 years	0.98	0.01	0.02	0.07	0.03	0.11	0.00	0.00
Method of contact; =1 if unknown	-0.63	0.00	0.00	0.07	0.03	0.03	0.26	0.00
constant	-0.72	-0.05	-0.06	-0.07	-0.03	-0.03	-0.01	0.05

Table 4: Coefficients and Cholesky matrix for the probability of completing the cascade, according to data from PASS Wessex

Parameter	Mean (log odds ratio)	Cholesky matrix				
		Sex; =1 if female	Degree; =1 if 1st degree	Method of contact; relative aged <18 years	Method of contact; =1 if unknown	Constant
Sex; =1 if female	0.55	0.14	0.00	0.00	0.00	0.00
Degree; =1 if 1st degree	-0.16	-0.01	0.15	0.00	0.00	0.00
Method of contact; relative aged <18 years	1.76	0.01	-0.01	0.17	0.00	0.00
Method of contact; =1 if unknown	2.73	0.01	-0.02	0.04	0.75	0.00
constant	-0.66	-0.07	-0.10	-0.04	-0.01	0.07

Cholesterol levels in relatives

This was a nationwide cascade screening programme which tested relatives of indexes with FH with cholesterol and genetic tests. In total, the Dutch dataset included data from 8,276 FH and 22,668 non-FH relatives. Figure 2 shows the distribution of PT-LDLC for FH and non-FH relatives who were not receiving LLT at the time of the cascade, by age. The LDLC distribution of the Dutch data was similar to available Welsh and Wessex data (Figure 11).

Table 5: Distribution of relatives by LDLC levels, according to the Dutch data

LDLC level, in mmol/L	age 0-17	age 18-39	age 40-59	age 60+
FH relatives				
0.00 – 1.00	SN	SN	SN	SN
1.01 – 2.00	67	55	19	11
2.01 – 3.00	382	305	121	54
3.01 – 4.00	821	741	357	139
4.01 – 5.00	894	979	534	134
5.01 – 6.00	492	606	370	113
6.01 – 7.00	206	255	160	60
7.01 – 8.00	59	104	70	20
8.01+	21	58	38	21
Not FH relatives				
0.00 – 1.00	44	48	25	14
1.01 – 2.00	1305	1101	521	199
2.01 – 3.00	1747	2946	2974	1348
3.01 – 4.00	314	1612	3377	1974
4.01 – 5.00	34	395	1336	789
5.01 – 6.00	SN	56	237	172
6.01 – 7.00	SN	8	50	22
7.01 – 8.00	SN	SN	10	SN
8.01+	SN	SN	SN	SN

LDLC: Low-Density Lipoprotein Cholesterol; FH: Monogenic Familial Hypercholesterolaemia. SN: supressed due to being a number below 7.

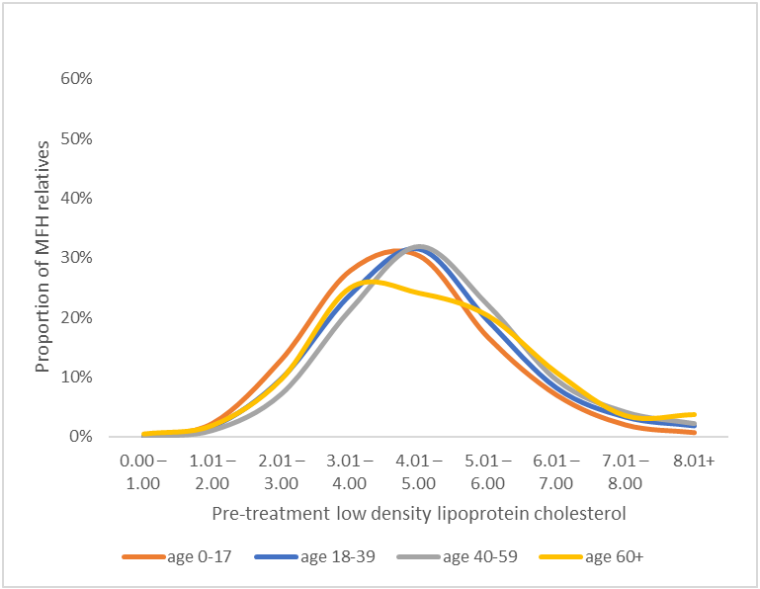


Figure 11A: Relatives with FH

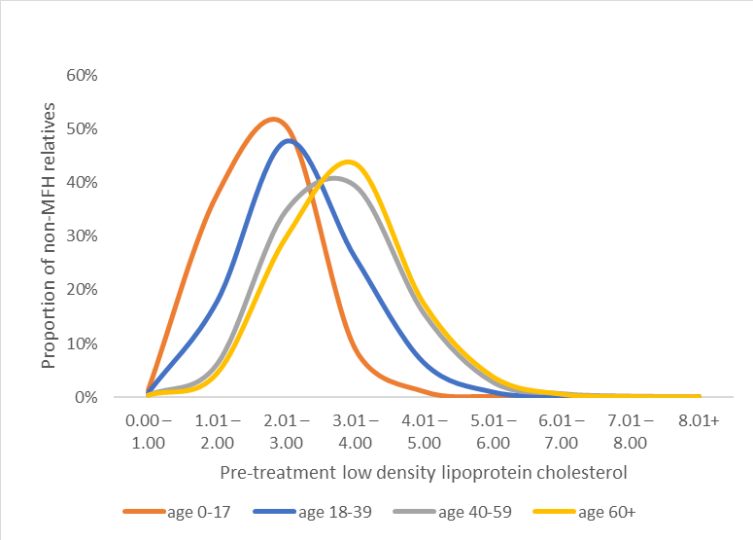
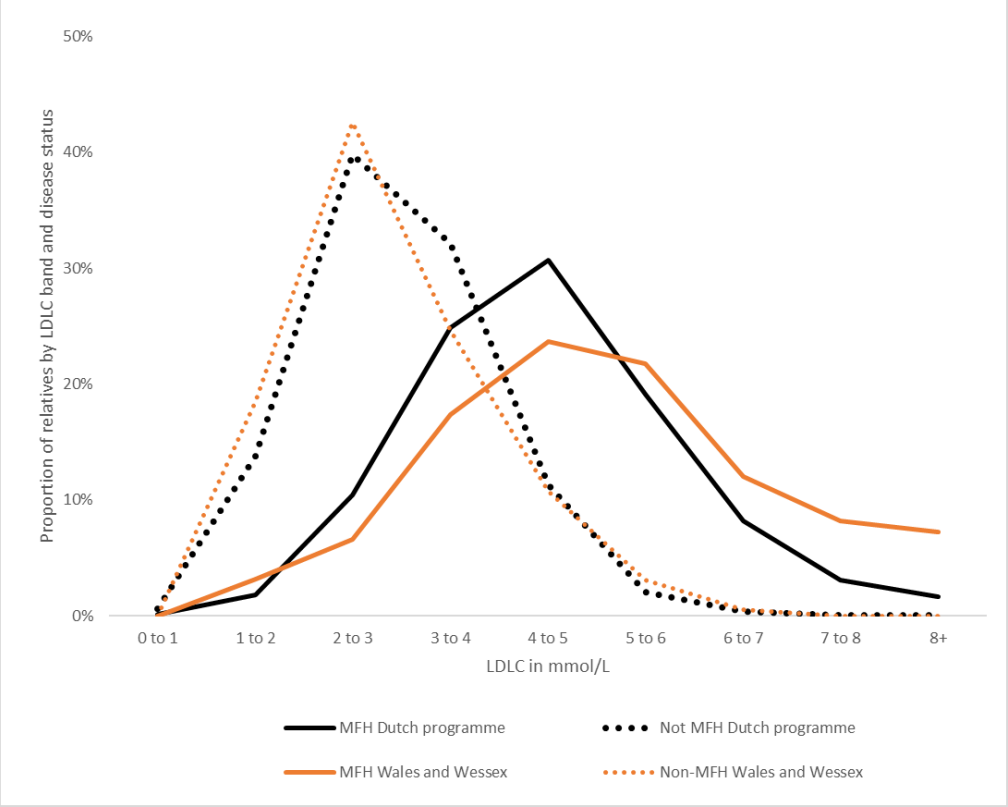


Figure 11B: Relatives without FH

Figure 11: Distribution of pre-treatment low density lipoprotein cholesterol (PT-LDLC) in relatives with FH (Panel A) and without FH (panel B) according to the data collected at the Dutch cascade screening programme

Figure 12: Comparison of LDLC distribution in relatives according to the Dutch and Welsh and Wessex data



LDLC: Low-Density Lipoprotein Cholesterol; FH: Monogenic Familial Hypercholesterolaemia.

Cascade costs

Table 6: Unit costs

Resource	Unit cost, £	Source
Medical consultant, per hour	109	PSSRU 2019 [3], hospital-based services – Consultant: medical
FH nurse/genetic counsellor per hour	56	PSSRU 2019 [3], hospital-based nurses – band 7
Secretarial assistance per hour	28	Calculated from PSSRU 2019 [3] assuming annual wage = £19,118, average between the lower and upper range of band 3 in 2019 from NHS Jobs
Letter	1.21	Gidlow et al (2019) [4]
Genetic test for index	305	Personal communication from Maggie Williams (Bristol Genetics Laboratory); prices for 2019/2020 by the Bristol Genetics Laboratory.
Genetic test for relative using blood sample	108	Personal communication from Maggie Williams (Bristol Genetics Laboratory); prices for 2019/2020 by the Bristol Genetics Laboratory.
Kit to do genetic test by post	13.64	Personal communication from Jane Breen (Royal Brompton and Harefield Hospital Trust) on June 2018: • Buccal swab kit: £10.72 • Jiffy bag: £1 • Documents: 10p • Postage: £1.81
Genetic test with mouth swab	92.4	Personal communication from Jane Breen (Royal Brompton and Harefield Hospital Trust) on June 2018:
Cholesterol test	£1	NHS Reference Costs 2019 [5]; Clinical biochemistry code DAPS04;
Blood sample collection	£4	NHS Reference Costs 2019 [5]; Phlebotomy code DAPS08

PSSRU: Personal Social Services Research Unit. RBHT: Royal Brompton and Harefield Trust

Table 7: Costs of selecting indexes to cascade

Outcome	Resources	Cost, £
Index assessed and not eligible	Arranging appointment to assess clinical score	5
	Appointment with consultant or FH nurse over 20 minutes to assess the index for their clinical score	19
	Total	23
Index assessed and eligible for clinical cascade	Arranging appointment to assess clinical score	5
	Appointment with consultant or FH nurse over 20 minutes to assess the index for their clinical score	19
	Arranging appointment to start the cascade	5
	Appointment to start cascade with FH nurse or genetic counsellor over 50 minutes	47
	Total	75
Index assessed and genetically tested and eligible for genetic cascade	Arranging appointment to assess clinical score	5
	Appointment with consultant or FH nurse over 20 minutes to assess the index for their clinical score	19
	Arranging appointment to do the genetic test	5
	Appointment to do genetic test, with FH nurse over 60 minutes	56
	Genetic test	305
	Communication of positive results and arranging appointment to start the cascade	5
	Appointment to start cascade with FH nurse or genetic counsellor over 50 minutes	47

	Total	446
Index assessed and genetically tested and NOT eligible for genetic cascade	Arranging appointment to assess clinical score	5
	Appointment with consultant or FH nurse over 20 minutes to assess the index for their clinical score	19
	Arranging appointment to do the genetic test	5
	Appointment to do genetic test, with FH nurse over 60 minutes	56
	Genetic test	305
	Communication of negative results	6
	Total	395

FH: Familial Hypercholesterolaemia

Table 8: Cost of testing relatives, summary

Outcome	**Resources**	**Cost, £**
Relative is seen by FH service but not tested	Appointment is arranged by secretarial staff.	5
	Relative is seen by the FH nurse or the genetic counsellor over 60 minutes.	56
	Total	61
Relative tested with the cholesterol test only	Appointment is arranged by secretarial staff.	5
	Relative is seen by the FH nurse or the genetic counsellor over 60 minutes.	56
	Blood sample for the cholesterol test	4
	Cholesterol test	1
	The relative is contacted by phone or letter with the results	6
	Total	72
Relative tested with the genetic test only	Appointment is arranged by secretarial staff.	5
	Relative is seen by the FH nurse or the genetic counsellor over 60 minutes.	56
	Blood sample for the genetic test	4
	Genetic test	108
	The relative is contacted by phone or letter with the results	6
	Total	179
Relative assessed with cholesterol test and with genetic test	Appointment is arranged by secretarial staff.	5
	Relative is seen by the FH nurse or the genetic counsellor over 60 minutes.	56
	Blood sample for the cholesterol test	4
	Cholesterol test	1
	Blood sample for the genetic test	4
	Genetic test	108
	The relative is contacted by phone or letter with the results	6
	Total	184

FH: Familial Hypercholesterolaemia

Further information on analytical methods

Step 1: Selecting combinations of testing strategies

To select the combinations of testing strategies to take forward, we ran all the testing strategies probabilistically over 1000 simulations through the decision tree which compared the testing strategies in relatives given their age, sex and FH status. We calculated the expected net benefit and probability that strategies were cost-effective given the age distribution of relatives who were tested and their age, the aforementioned thresholds and prevalence of FH of 50% and 25%. These values reflect the upper and lower prevalence bounds for concomitant and sequential cascade given the proportion of FH indexes selected to the cascade. We selected the strategies with highest net benefit and those with a probability of being cost-effective ≥ 5% in each age group and combined them to create testing strategies. We also created "harmonised testing strategies", composed of the same unique strategy across age groups.

Step 2: Cost-effectiveness of cascade protocols

We ran the full cost-effectiveness model on the selected testing strategies, together with the standard testing strategy in the Welsh and Wessex services of offering genetic testing to all relatives, as well as a variation to this strategy where relatives who are on LLT are assumed to have FH while relatives who are not on LLT are genetically tested. The model combines each testing strategy with the options for contacting relatives (direct or indirect, concomitant or sequential cascade) and with the options for selecting indexes (in the base-case, WDLCN≥ 6, etc.).

Scenario analysis

Table 9: Scenarios and their rationale

Base-case	Scenario	Rationale
Scenarios related to the cascade		
WDLCN based on PASS Wales data is the clinical score used to screen indexes prior to the genetic test or to select indexes to the cascade. Using PASS Wales data to inform the relatives' characteristics.	Using AWDLCN based on PASS Wales data as the clinical score.	AWDLCN is the clinical score used in the Welsh FH service in parallel with WDLCN.
	Using the Simon Broome criteria based on PASS Wessex data as the clinical score. Using PASS Wessex data to inform the relatives' characteristics.	The Simon Broome criteria is proposed by the 2019 NICE CG71 [6] and a modified version is used by the FH Wessex service.
The proportion of FH relatives with no prior CV history who are on LLT at the time of the cascade was obtained from the PASS Wessex data.	The proportion of FH relatives with no prior CV history on LLT obtained from PASS Wales.	It reflects the proportion of relatives on LLT according to what was observed in the FH Welsh service.
	The proportion of FH relatives with no prior CV history on LLT obtained from general population data.	Assumes that FH relatives who are not diagnosed have the same probability of being on LLT as the general population.
Out-of-area relatives are not cascaded.	Out-of-area relatives are cascaded, with their numbers informed by PASS Wales.	To explore the impact of ensuring national access to cascade testing services for FH.
	Out-of-area relatives are cascaded, with their numbers informed by PASS Wessex.	
To conduct the genetic test, the relatives have a blood sample taken at the FH service.	The genetic test is conducted on a saliva swab taken by the relative and sent to the FH service by post.	The Harefield Hospital offers this postal service to relatives who are out of area.
In testing strategies where relatives have a cholesterol test and a genetic test, taking the second blood sample does not require an additional nurse appointment.	In testing strategies where relatives have a cholesterol test and a genetic test, taking the second blood sample requires an additional nurse appointment.	As this type of testing strategies are not implemented in the Wales and Wessex FH services, there is uncertainty about the resources involved in their implementation, and an nurse appointment may be required in addition to the cost of having a blood sample taken.
The proportion of VUS reclassified to pathogenic out of those reclassified corresponds to the probability that VUS are reclassified.	Assuming that the VUS not yet reclassified are not FH.	Assumes that VUS not yet reclassified are not pathogenic.
Indexes with VUS are not selected to the cascade. Of those who have FH, their relatives are not contacted.	Indexes with VUS are selected to the cascade and their affected relatives tested and managed as if they had FH.	To ascertain the magnitude of benefits and costs if indexes with VUS were selected to the cascade and their relatives tested and managed as if they had FH.
The prevalence of FH in 1st degree relatives is 50% and in 2nd degree relatives is 25%, given the autosomal dominant inheritance pattern.	The prevalence of FH is estimated from the PASS Welsh data.	Relatives who come forward for testing may be a selected population at higher risk of FH, as observed in the PASS Welsh and Wessex data.
	The prevalence of FH is estimated from the PASS Wessex data.	
Scenarios related to the long-term model		

Base-case	Scenario	Rationale
Non-FH relatives at high CV risk not on LLT who are misdiagnosed with FH do not have health benefits from treatment.	Non-FH relatives at high CV risk not on LLT and who are misdiagnosed with FH benefit from treatment.	Non-FH relatives at high CV risk who are not on LLT at the time of the cascade are likely to benefit from FH diagnosis and treatment given their high CV risk.
FH relatives have the same LDLC reduction from LLT if they were diagnosed as FH in the cascade or if they were on LLT prior to the cascade.	FH relatives who are diagnosed have their LDLC reduced by 50%, whereas FH relatives who are on LLT at the time of the cascade have the LDLC reduction observed post-LLT in the CPRD cohort.	FH relatives who are on LLT at the time of the cascade may not have been diagnosed with FH; upon diagnosis with FH, they may have further LDLC reductions.
FH relatives who are diagnosed and/or are on LLT at the time of the cascade have the LDLC reduction observed post-LLT in the CPRD cohort.	FH relatives on are on LLT have their LDLC reduced by 50% in line with the NICE CG71 [6].	The NICE clinical guideline on FH diagnosis and management recommends a treatment target of 50% reduction in LDLC [ref].
	FH relatives on are on LLT have their LDLC reduced to the EAS targets [7].	The 2019 EAS guideline recommends LDLC targets of 3.5 mmol/L for children and adolescents and 1.8 mmol/L for adults [7].
The extrapolation of CV risk over time was based on the generalised gamma survival model.	The extrapolation of CV risk over time was based on the exponential survival model.	The exponential model provided extrapolations of the risk of the 1st major CV event that were consistent with the Perak et al observations [8].
Including LDLC burden in that the effect of LDLC reductions on CV risk increases over time as proposed by the 2017 EAS Consensus Statement [9].	Excluding LDLC burden in that the effect of LDLC reduction on CV risk is constant over time and corresponds to the effect observed in the CTTC meta-analyses [10].	The LDLC effect size is uncertain, with the estimate of the effect of LDLC reductions on CV risk from the CTTC meta-analysis being a conservative estimate [10]..
CV risk increases over time as inferred by comparing CV rates over different follow-up periods from the Perak et al study [8]..	CV risk increases over time with age, as inferred using the standardised mortality ratios obtained comparing FH patients to the general population [11].	The follow-up period of the CPRD cohort is too short to reliably predict CV risk over the long-term. While Perak et al can be used to adjust CV risk, it is based on a cohort of patients diagnosed retrospectively with FH given their elevated cholesterol in the US. The alternative is to use a British cohort and assume that the standardised mortality ratios compared to the general population correspond to the increase in fatal and non-fatal CV risk with age.
Monitoring costs of patients diagnosed as FH obtained from the base-case long-term model.	Assuming low costs of monitoring patients with FH.	To reflect the variability of monitoring practices across the UK.
	Assuming high costs of monitoring patients with FH.	

AWDLCN: Age-adjusted Welsh-modified Dutch Lipid Clinic Network criteria; CPRD: Clinical Practice Research Datalink; CTTC: Cholesterol Treatment Trialists Collaboration; CV: Cardiovascular; EAS: European Atherosclerosis Society; FH: Familial Hypercholesterolaemia; LDLC: Low-Density Lipoprotein Cholesterol; LLT: Lipid Lowering Treatment; FH: Monogenic Familial Hypercholesterolaemia; VUS: Variant of Unknown Significance; WDLCN: Welsh-modified Dutch Lipid Clinic Network criteria.

4. Validation

The senior health economist in the team, who was not involved in writing the code, investigated the model and produced a validation report. The investigation included validation of worksheets that contained calculations or inputs and review of the VBA code which operates the decision trees. In addition, the various intermediate tables generated in the VBA code were re-generated by hand within an excel worksheet to check that the code was performing as expected. This validation exercise detected some issues in the conceptualisation of some elements of the model and issues around its implementation. Of note:

- Conceptualisation: the model originally considered the whole population of indexes who were tested by the Wales and Wessex FH services, although only indexes with scores above a specific threshold (e.g. WDLCN >= 6) are routinely tested; hence the prevalence of FH in indexes with scores below these thresholds may not be generalisable. The model was revised to include only the indexes with scores higher than the thresholds used to determine testing.
- Input data: minor errors in the selection of input data and in the implementation of the random draws from the distribution of inputs, which were subsequently corrected.
- Module for stage 3: minor error in the coding of module 3, relating to the calculation of QALYs, which was subsequently corrected.
- Module for stage 2: minor error in adding the cost of directly contacting relatives, minor errors in the calculation of the outcomes per index from the intermediate arrays; all were subsequently corrected.
- Module for linking the outcomes from relatives to indexes: error in that the code did not account for the prevalence of FH in relatives of FH indexes from module 2; error in that the calculation of probabilities assumed that the prevalence of FH in all relatives was 50%; error in that the outcomes of relatives of indexes who were not selected were calculated as per relative than per index; error in that the calculation of the cost of diagnosis was based on the prevalence of indexes with FH rather than the proportion of tested indexes with FH; these errors were subsequently corrected.

Based on the validation report, the main modeller revised the model to correct the errors.

The validation report proposed a number of validation tests, which were implemented in the model and produced the expected results (see *Details on E1: Have any other validation techniques been performed* below).

The main modeller generated the intermediate and results tables for two cascade protocols by hand to confirm that the code was performing as expected.

- Using the WDLCN score to select indexes to the cascade who score >= 6; cascade pattern = sequential; method of contact = direct; testing strategy = N1_H4_L_T1;
- Using the WDLCN score to select indexes to the cascade who score >= 6; cascade pattern = concomitant; method of contact = direct; testing strategy = N5_H_L_T0.

This process revealed an error in the code to calculate the probability that non-FH relatives were misdiagnosed, which was corrected.

The lead analyst responsible for the analysis of the PASS data checked the inputs derived from this analysis.

The main modeller applied the AdVISHE and TECH-VER checklists [12,13] (see next sections for results).

Advishe checklist [13]

Table 10: Advishe checklist for the cost-effectiveness model on cascade protocols

Question	Answer
Part A: Validation of the conceptual model	
A1: Have experts been asked to judge the appropriateness of the conceptual model?	Yes, the stakeholder group agreed that the conceptual model was appropriate.
A2: Has this model been compared to other conceptual models found in the literature or clinical textbook?	Yes, we compared our conceptual model to other models in the literature. Including the selection of indexes to the cascade in the cascade process is in line with previous cost-effectiveness analyses of cascade testing [14-16]. Similar to the cost-effectiveness analysis that informed the 2008 NICE CG71 on FH [6,16], we included genetic testing and LDLC testing strategies. The model structure was broadly similar to previous cost-effectiveness analysis of cascade screening. For example, Nherera et al and Crosland et al structured the diagnostic element of the model as a decision tree [14,16]. While in the Crosland et al model, the calculation of the long-term consequences of diagnosis is part of the cost-effectiveness model, in Nherera et al the long-term consequences were calculated in separate Markov models and used to inform the diagnosis model, similarly to our model [14,16].
Part B: Input data validation	
B1: Have experts been asked to judge the appropriateness of the input data?	Yes, the experts agreed that the input data was appropriate
B2: When input parameters are based on regression models, have statistical tests been performed?	The only input based on a regression model is the probability that relatives are tested, given their characteristics and the method of the contact. Statistical tests to this regression model are reported in Chapter *Service Data Analysis* on the analysis of the PASS databases.
Part C: Validation of the computerised model	
C1: Has the computerised model been examined by modelling experts?	Yes, the computerised model was examined by Beth Woods. BW is not an independent expert as she supervised the development of the cost-effectiveness model and collaborated in all economic analyses. The cost-effectiveness model is valid.
C2: Has the model been run for specific, extreme sets of parameter values in order to detect any coding errors?	Yes, the tests are reported in the TECH-VER checklist below.
C3: Have patients been tracked through the model to determine whether its logic is correct?	Yes, the cohort was checked at the end of each module to ensure consistency.
C4: Have individual submodules of the computerised model been tested?	Yes, each module was tested by reproducing the calculations in the Excel sheet for two strategies.
Part D: Operational validation	
D1: Have experts been asked to judge the appropriateness of the model outcomes?	Yes, the stakeholder group reviewed the predictions of the model for patients diagnosed with FH and agreed that these had face validity.
D2: Have the model outcomes been compared to the outcomes of other models that address similar problems?	Yes, similarly to previous models, we found that cascade testing is cost-effective compared to no cascade [14-21].

D3: Have the model outcomes been compared to the outcomes obtained when using alternative input data?	Yes, in the scenario analysis. We conducted a scenario analysis using PASS Wessex data to inform all cascade model inputs informed by the PASS Wales data as far as data were available. We conducted various scenarios with alternative assumptions regarding the prediction of long-term consequences of diagnosis in FH and non-FH relatives.
D4: Have the model outcomes been compared to empirical data?	Yes, we compared the number of FH relatives diagnosed with the genetic test per FH index selected to the cascade if relatives are contacted directly or indirectly compared to what we have observed in the PASS Wales data. Details below. In sum, there were differences if using the predicted probability of completing the cascade, explained by the differences in the predicted probability of completing the cascade according to the contact method vs observed in the relatives' population and the observed prevalence of FH in 1st and 2nd degree relatives. See *Details on D4: Have the model outcomes been compared to empirical data* below.
Part E: Other validation techniques	
E1: Have any other validation techniques been performed?	Yes, we devised six validation tests, which the model has passed. See *Details on E1: Have any other validation techniques been performed b*elow.

FH: Familial Hypercholesterolaemia; LDLC: Low-Density Lipoprotein Cholesterol; FH: Monogenic Familial Hypercholesterolemia; QALYs: Quality-Adjusted Life Years; TECH-VER: TECHnical VERification checklist;

Details on D4: Have the model outcomes been compared to empirical data

In the PASS Wales data, we observed 0.83 FH 1st degree relatives diagnosed and 0.46 2nd or over degree relatives per FH index selected to the cascade (total = 1.35 FH relatives diagnosed per FH index selected to the cascade).

Using the predicted probability of completing the cascade according to the regression model for direct or indirect contact, the assumed prevalence of FH in relatives, and the observed number of 1st degree relatives contacted per FH index selected and 2nd degree relatives contacted per 1st degree FH relative diagnosed, the model underpredicts the number of FH relatives diagnosed at 1.13 under direct contact and 0.83 under indirect contact, assuming a sequential cascade. However, we predicted the same number of 1st degree relatives if the observed probability of completing the cascade is used, the observed prevalence of FH in 1st degree relatives, and the observed number of 1st degree relatives contacted per FH index selected to the cascade.

Assuming a sequential cascade, and using the observed probability of completing the cascade, the observed prevalence of FH in 2nd degree relatives, and the observed number of 2nd degree relatives per 1st degree relative diagnosed with FH, the model underpredicts the number of 2nd degree relatives with diagnosed at 0.39. If we calculate the number of 2nd degree FH relatives diagnosed directly from the number of 2nd degree relatives per FH index selected, their probability of completing the cascade and their prevalence of FH, our predictions match the observed data.

Details on E1: Have any other validation techniques been performed

1. We checked that the same number and profiles of patients are being counted in each policy by setting the long-term costs and QALYs the same irrespective of diagnosis but differing by patient characteristics. We confirmed that the long-term costs and QALYs were the same across all strategies.
2. We checked that the strategies with and without genetic testing worked in the same way by modifying the LDLC distributions so that LDLC at a specific cut-off is a perfect test. We

confirmed that the strategies without genetic testing had the same outcomes as the strategies with genetic testing.

3. We checked that the strategies using direct or indirect contact differed only in the probability of completing the cascade and cost, by setting the effect and the cost of direct contact to zero. We confirmed that strategies using direct or indirect contact had the same outcomes, QALYs and costs.
4. We checked that the sequential and concomitant strategies differed only due to the attrition of the 1st degree relatives, by setting the probability of completing the cascade to 1. We confirmed that the same testing strategy but differing cascade type results in the same outcomes, QALYs and costs.
5. We checked that the index strategies were operating as expected by setting the prevalence of FH in indexes the same independent of the clinical scores. We confirmed that the outcomes were the same across the index strategies.
6. We checked that the index strategies were operating as expected by assuming that all indexes with a score above a specific level have FH and non below this level had FH. We confirmed that index strategies involving genetic testing then had the same outcomes as index strategies not involving genetic testing.
7. We checked that the number of FH relatives correctly diagnosed corresponded to the number of FH relatives per index assessed to the cascade (0.59 relatives) and per index with FH (2.08 relatives) if indexes with VUS are cascaded and all relatives complete the cascade.

TECH-VER checklist

Table 11: TECH-VER checklist [12]

Test description	Expected result	Result
Pre-analysis calculations		
Does the technology (drug/device, etc.) acquisition cost increase with higher prices?	Yes	Yes, tested by increasing the cost of the genetic test in relatives.
Does the probability of an event, derived from an OR/RR/HR and baseline probability, increase with higher OR/RR/HR?	Yes	Yes, tested by increasing the OR associated with direct method of contact.
Event-state calculations		
The sum of the expected probabilities of the terminal nodes should sum up to 1	Yes	Yes. Tested by summing the predicted probabilities by the decision trees in Module 1.
Are costs zero if all costs are set to zero?	Yes	Yes. Tested by setting all cascade testing costs to zero and running the full model (Module 4); the cost of diagnosis of zero for all strategies.
If all decision options have the same effectiveness and costs, are all results the same?		Yes. See validation test 1 in table 19.
Result calculations		
Do the more effective decision options yield greater QALYs and life years?	Yes	Yes. Cascade options using direct method of contact, concomitant cascading, more intensive use of genetic testing, and more expansive selection of indexes reach more relatives and yield greater QALYs.
Do the more costly decision options yield greater treatment costs?	Yes	Yes. Cascade options using

		genetic testing are more costly and yield greater total costs.
Do the disaggregated results sum to the total results?	Yes	Yes. In module 4, the total results per index equal the sum of results per FH index and results per non-FH index. In module 2, the total results per FH index equal the sum of results in FH relatives and in non-FH relatives.
The reported ICERs in the fully incremental analysis are non-decreasing	Yes	Yes, as per cost-effectiveness frontier
Uncertainty analysis		
Do all parameters used in the sensitivity analysis have appropriate associated distributions – upper and lower bounds should surround the deterministic value (i.e. upper bound ≥ mean ≥ lower bound)	Yes	Yes.
Standard error and not standard deviation used in sampling	Yes	Yes
Lognormal/gamma distribution for HRs and costs/resource use	Yes	Yes
Beta for utilities and proportions/probabilities	Yes	Yes
Dirichlet for multinomial	Yes	Yes
Multivariate normal for correlated inputs	Yes	Yes
Normal for other variables as long as samples do not violate the requirement to remain positive when appropriate	Yes	Yes: lognormal for rate ratios.
Check PSA output mean costs, QALYs, and ICER compared with the deterministic results. Is there a large discrepancy?	No	No, the results are similar.
If you take new PSA runs from the Microsoft Excel model do you get similar results?	Yes	Yes.
Is(are) the CEAC line(s) in line with the cost-effectiveness scatter plots and the efficient frontier?	Yes	CEAC calculated but not drawn given large number of strategies. CEAF compared to results and efficiency frontier; found to consistent.
Does the PSA cloud demonstrate an unexpected behaviour or have an unusual shape?	No	Not examined given the large number of strategies.
Is the sum of all CEAC lines equal to 1 for all WTP values?	Yes	Yes.
Do the explored scenario analyses provide a balanced view on the structural uncertainty (i.e. not always looking at more optimistic scenarios)?	Yes	Yes, see scenario analysis.
Are the scenario analysis results plausible and in line with a priori expectations?	Yes	Yes, see scenario analysis.
Check the correlation between two PSA results (i.e. costs/QALYs under the SoC and costs/QALYs under the comparator). Should be very low (very high) if different (same) random streams are used for different arms	High	Checked in the file with the cost and QALYs simulations. Correlation is 1 or close to 1 as the same random streams are used for each arm.
Do sensitivity analyses include any parameters associated with methodological/structural uncertainty?	Yes	Yes, see scenario analysis.
Value of information analysis if applicable: Was this implemented correctly?	Yes	Yes, checked in the VBA code.
Value of information analysis if applicable: Which types of analysis?		EVPI only.
Check if all sampled input parameters in the PSA are correctly linked to the corresponding event/state calculations	Yes	Yes, via input sheet.

CEAC: Cost-Effectiveness Acceptability Frontier; EVPI: Expected Value of Perfect Information; HR: Hazard Ratio; ICER: Incremental Cost-Effectiveness Ratio; OR: Odds Ratio; FH: Monogenic Familial Hypercholesterolaemia; PSA: Probabilistic Sensitivity Analysis; RR: Risk Ratio; QALYs: Quality-Adjusted Life Years; WTP: Willingness-To-Pay.

5. Results

For the base-case, we present the following results:

- Cost-effectiveness plane, frontier and acceptability frontier for all the cascade protocols, and health outcomes and costs of the protocols in the cost-effectiveness frontier.
- Cost-effectiveness plane and frontier for the cascade protocols using harmonised testing strategies, and health outcomes and costs of the protocols in the cost-effectiveness frontier.
- Expected value of perfect information per index family assessed to the cascade.

For the scenario where genetic testing is not available:

- Health outcomes and costs of the protocols in the cost-effectiveness frontier.
- Comparison of the health outcomes and costs of the protocols with the highest net health gain in this scenario to the base-case cost-effective protocols.

For the scenario analysis:

- Relatives' testing strategies put through the full cost-effectiveness analysis.
- Scenarios where the protocol with the highest net health gain did or did not change from the base-case cost-effective protocol.

Base-case results

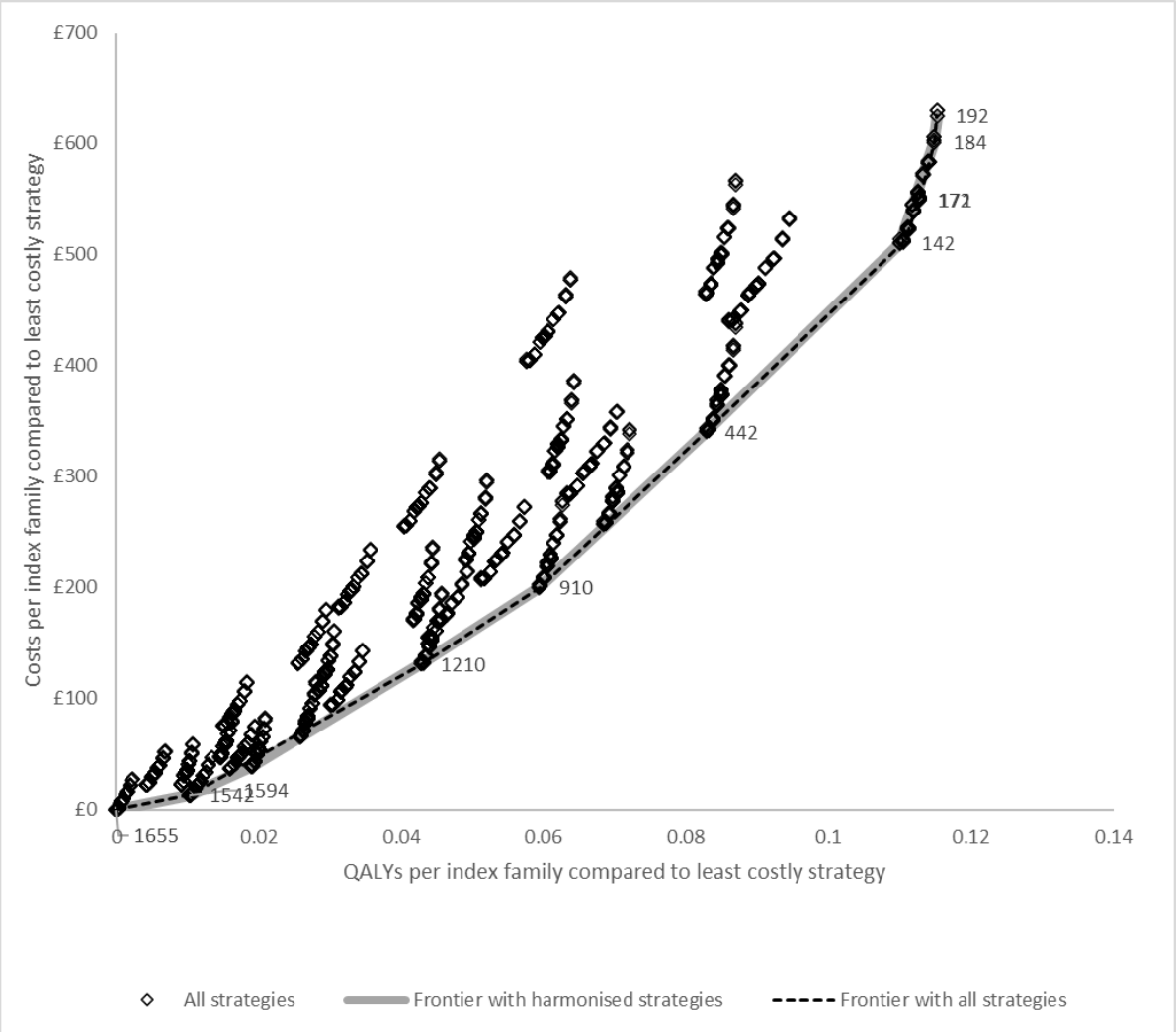


Figure 13: Cost-effectiveness plane and frontier for the base-case (probabilistic results)

See next page for legend.

Table 12: Protocols in the cost-effectiveness frontier

Type of index strategy	WDLCN cut-off	Cascade pattern	Method of contact	Testing strategies, by age					Label in graph	Sensitivity	Cost of diagnosis
				Age 0-9	**Age 10-17**	**Age 18-39**	**Age 40-59**	**Age 60+**			
Select indexes to the genetic test; cascade relative from indexes with FH mutation	12	sequential	indirect	N3_H5_L3_T1					1655	0.11	£98
			direct	N3_H6_L3_T1					1594	0.15	£109
	10			N3_H5_L3_T1			N2_H3_L_T1	N3_H6_L2_T0	1542	0.16	£110
	9	concomitant		N3_H6_L3_T1					1210	0.27	£200
	7			N3_H5_L3_T1		N3_H6_L3_T1	N2_H3_L_T1	N3_H6_L2_T1	910	0.33	£258
	6			N3_H6_L3_T1					442	0.41	£380
				N3_H5_L3_T1		N3_H6_L3_T1	N2_H3_L_T1	N3_H6_L2_T1	142	0.51	£530
				N3_H5_L3_T1		N3_H6_L3_T1	N2_H2_L_T1	N3_H6_L2_T1	145	0.52	£536
				N3_H5_L3_T1	N3_H5_L2_T1	N3_H6_L3_T1	N2_H2_L_T1	N3_H6_L2_T1	172	0.53	£542
				N3_H5_L3_T1	N3_H5_L2_T1	N3_H6_L3_T1	N2_H2_L_T1	N3_H5_L1_T1	171	0.53	£542
				N3_H6_L2_T1					184	0.55	£559
				N5_H_L_T1	N5_H_L_T1	N5_H_L_T1	N5_H_L_T1	N5_H_L_T1	192	0.56	£573

Strategies starting with N3 are strategies where relatives who are not on LLT are tested for their LDLC, with relatives whose LDLC ≥ higher cut-off are assumed to have FH, relatives with LDLC between the higher and the lower cut-off are genetically tested, and relatives with LDLC < lower cut-off are assumed not to have FH.

Strategies starting with N2 are strategies where relatives who are not on LLT are tested for their LDLC, with relatives whose LDLC ≥ higher cut-off are genetically tested, and relatives with LDLC < higher cut-off are assumed not to have FH.

The number next to the letter "H" represents the higher cut-off for LDLC.

The number next to the letter "L" represents the lower cut-off for LDLC, where applicable.

Strategies terminating in T1 assume that relatives who are on LLT at the time of the cascade have FH without further testing.

WDLCN: Welsh-modified Dutch Lipid Clinic Network.

Table 13: Protocols in the cost-effectiveness frontier if only including harmonised testing strategies

Type of index strategy	WDLCN cut-off	Cascade pattern	Method of contact	Testing strategies, by age					Sensitivity	Cost of diagnosis
				Age 0-9	**Age 10-17**	**Age 18-39**	**Age 40-59**	**Age 60+**		
Select indexes to the genetic test; cascade relative from indexes with FH mutation	12	sequential	indirect	N3_H5_L3_T1					0.11	£98
	12		direct	N3_H6_L3_T1					0.15	£109
	12	concomitant		N3_H6_L3_T1					0.19	£126
	10			N3_H6_L3_T1					0.27	£200
	9			N3_H6_L3_T1					0.33	£257
	7			N3_H6_L3_T1					0.41	£380
	6			N3_H6_L3_T1					0.51	£529
	6			N3_H6_L2_T1					0.55	£559
	6			N5_H_L_T1					0.56	£573

Testing strategies starting with N3 are strategies where relatives who are not on LLT are tested for their LDL-C, with relatives whose LDL-C ≥ higher cut-off are assumed to have FH, relatives with LDL-C between the higher and the lower cut-off are genetically tested, and relatives with LDL-C < lower cut-off are assumed not to have FH.

Strategies starting with N2 are strategies where relatives who are not on LLT are tested for their LDL-C, with relatives whose LDL-C ≥ higher cut-off are genetically tested, and relatives with LDL-C < higher cut-off are assumed not to have FH.

The number next to the letter "H" represents the higher cut-off for LDL-C.

The number next to the letter "L" represents the lower cut-off for LDL-C, where applicable.

Strategies terminating in T1 assume that relatives who are on LLT at the time of the cascade have FH without further testing.

The cascade testing strategies highlighted in yellow form the cascade protocol with the highest net health gain at the cost-effectiveness threshold of £15,000/QALY, while the testing strategies highlighted in green form the cascade protocol with the highest net health gain at the cost-effectiveness threshold of £20,000/QALY.

QALYs: Quality Adjusted Life Years; WDLCN: Welsh-modified Dutch Lipid Clinic Network.

Scenario where genetic testing is not available or its capacity is constrained

Table 14: Strategies forming the cost-effectiveness frontier

WDLCN cut-off	Type of cascade	Method of contact	Testing strategies by age					QALYs vs cheapest	Costs vs cheapest	ICER/ QALY
			Age 0-9	Age 10-17	Age 18-39	Age 40-59	Age 60+			
12	sequential	Indirect	N1_H4_L_T1		N1_H5_L_T1		N1_H4_L_T1	0.000	£0	
		Direct	N1_H4_L_T1		N1_H5_L_T1		N1_H4_L_T1	0.006	£5	£905
10			N1_H4_L_T1		N1_H5_L_T1		N1_H4_L_T1	0.019	£38	£2,489
	simultaneous		N1_H4_L_T1		N1_H5_L_T1		N1_H4_L_T1	0.028	£65	£2,880
9			N1_H4_L_T1			N1_H5_L_T1	N1_H4_L_T1	0.037	£109	£4,868
			N1_H4_L_T1		N1_H5_L_T1		N1_H4_L_T1	0.059	£222	£5,130
			N1_H4_L_T1			N1_H5_L_T1	N1_H4_L_T1	0.074	£323	£6,964
			N1_H4_L_T1		N1_H5_L_T1		N1_H4_L_T1	0.089	£476	£9,915
			N1_H4_L_T1			N1_H5_L_T1	N1_H4_L_T1	0.104	£664	£12,578
			N1_H4_L_T1					0.115	£853	£18,140
			N1_H4_L_T1				N1_H3_L_T1	0.116	£900	£28,601
			N1_H3_L_T1		N1_H4_L_T1		N1_H3_L_T1	0.127	£1,280	£36,570
6			N1_H3_L_T1				N1_H2_L_T1	0.138	£2,461	£102,386

Table 15: Comparison between base-case cost-effective strategies and cost-effective strategies if genetic testing is not available

			Genetic testing not available		Genetic testing available	
	Result	No Cascade	Cost-effective at £15,000/QALY	Cost-effective at £20,000/QALY	Cost-effective at £15,000/QALY	Cost-effective at £20,000/QALY
WDLCN cut-off		NA	6	6	6	6
Type of cascade			Simultaneous	Simultaneous	Simultaneous	Simultaneous
Method of contact			Direct	Direct	Direct	Direct
Testing strategy	age 0-9		N1_H4_L_T1	N1_H4_L_T1	N3_H5_L3_T1	N3_H5_L3_T1
	age 10-17		N1_H4_L_T1	N1_H4_L_T1	N3_H5_L3_T1	N3_H5_L2_T1
	age 18-39		N1_H4_L_T1	N1_H4_L_T1	N3_H6_L3_T1	N3_H6_L3_T1
	age 40-59		N1_H5_L_T1	N1_H4_L_T1	N2_H2_L_T1	N2_H2_L_T1
	age 60+		N1_H4_L_T1	N1_H4_L_T1	N3_H6_L2_T1	N3_H6_L2_T1
Result 1			0.413	0.445	0.518	0.531
Result 2			0.244	0.263	0.307	0.314
Result 3			0.139	0.167	0.024	0.025
Result 4			£388	£388	£538	£544
Result 5			0	0	1.450	1.506
Result 6		10.791	10.918	10.928	10.936	10.937
Result 7		£3,012	£2,988	£2,994	£3,112	£3,133
Result 8		114.067	114.193	114.204	114.211	114.213
Result 9		£13,557	£14,265	£14,454	£14,207	£14,235
Result 10		113.163	113.242	113.240	113.264	113.264
Result 11		113.389	113.480	113.481	113.501	113.501

Results are deterministic.

QALY: Quality-Adjusted Life Year. WDLCN: Welsh-modified Dutch Lipid Clinic Network criteria.

Legend for results:

1. Sensitivity, that is, probability that a relative with monogenic familial hypercholesterolaemia (FH) is correctly diagnosed with familial hypercholesterolaemia (FH).
2. Number of FH relatives diagnosed with FH.
3. False positive rate, that is, the probability that a non-FH relative is misdiagnosed with FH.
4. Cost of diagnosis per index assessed, from assessing the index to testing the relatives.
5. Number of genetic tests (index and relatives) per index assessed.
6. Long-term health outcomes of MFH relatives, in quality-adjusted life years (QALYs)
7. Long-term costs of MFH relatives
8. Total health outcomes of all relatives, in QALYs.
9. Total costs of all relatives.
10. Net health benefit at a cost-effectiveness threshold of £15,000/QALY.
11. Net health benefit at a cost-effectiveness threshold of £20,000/QALY.

Probabilistic sensitivity analysis

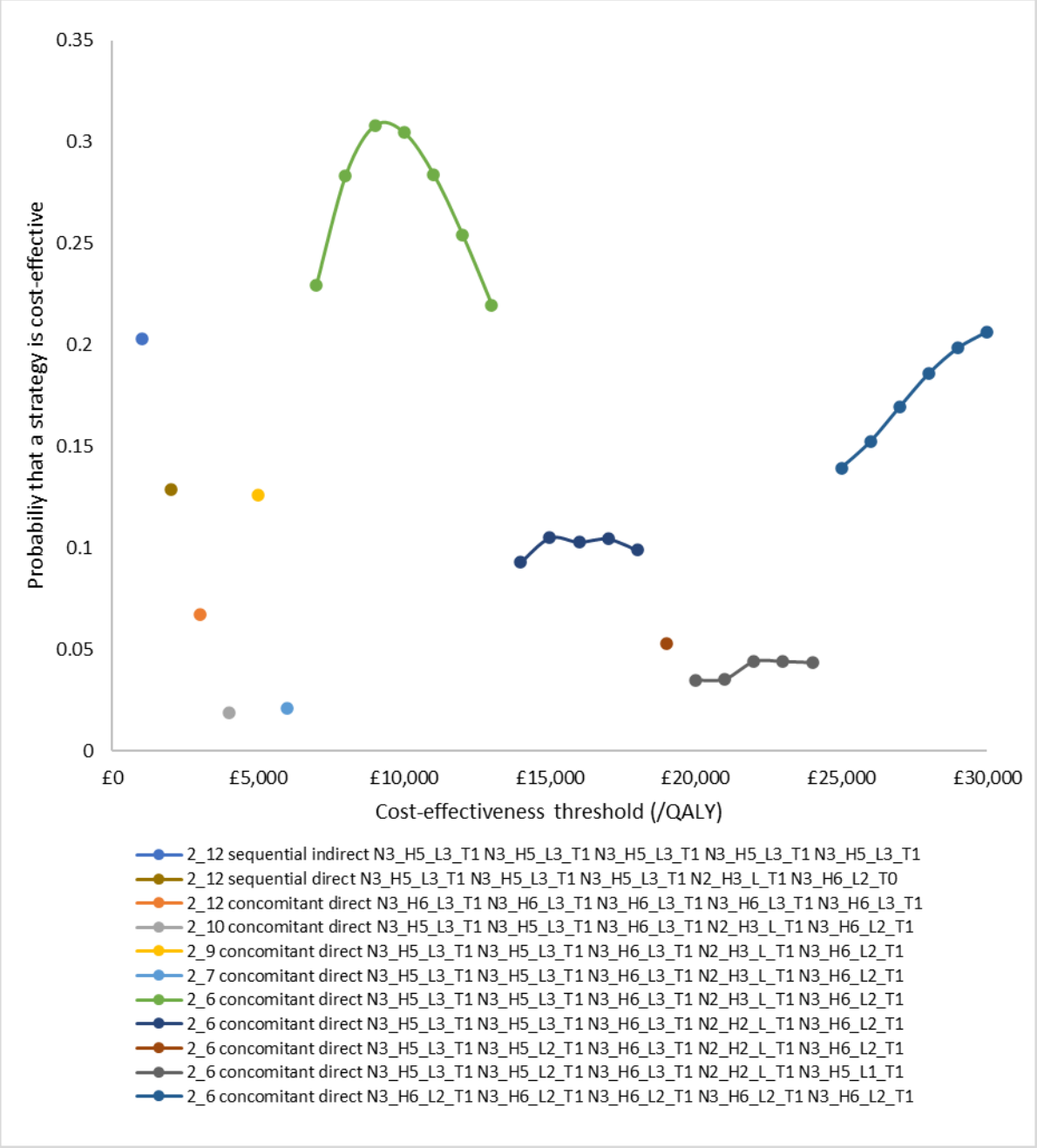


Figure 14: Cost-effectiveness acceptability frontier

Legend:
"2_12" to "2_6" stands for the strategy to select indexes to the cascade, with "2" representing a strategy where indexes are screened to the genetic test according to their clinical score (in the base-case, Welsh-adjusted Dutch Lipid Clinic Network criteria"; the number "12" to "6" represents the cut-off.
"Concomitant cascade" refers to the simultaneous contact of 1st and 2nd degree relatives.

Expected value of perfect information

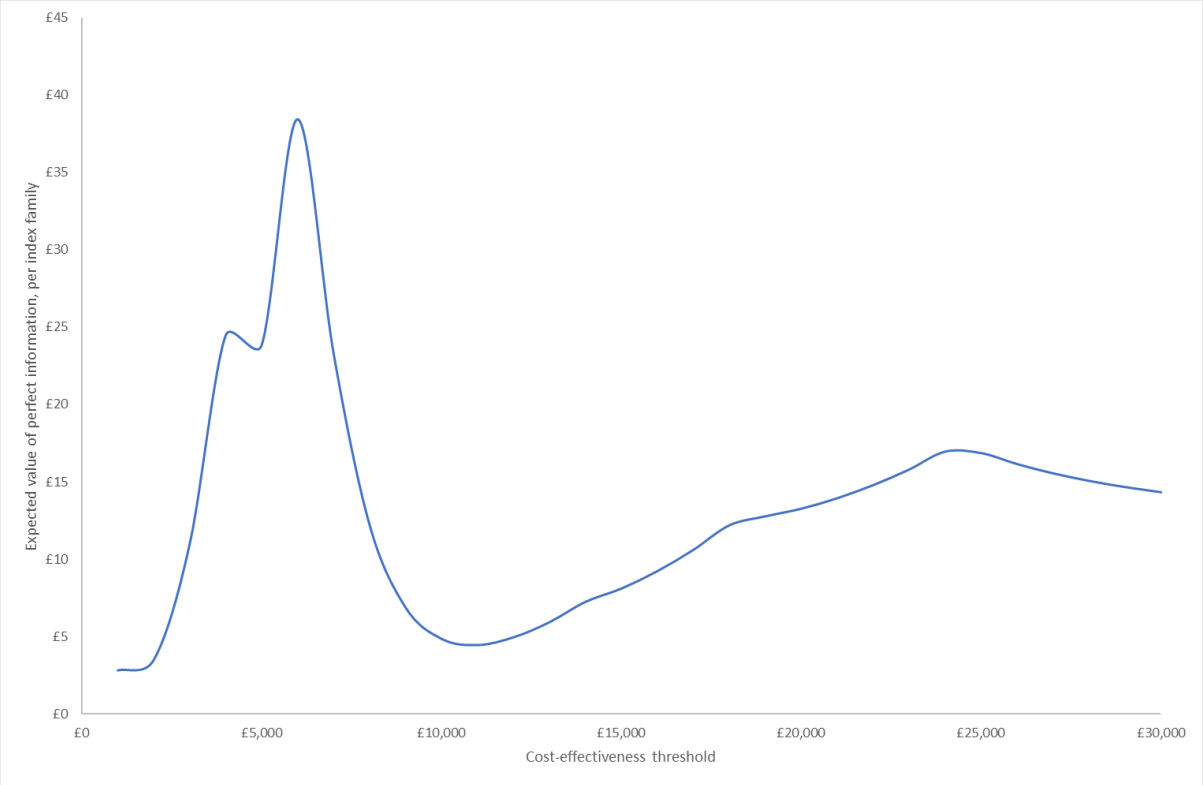


Figure 15: Expected value of perfect information per index assessed to the cascade over a range of cost-effectiveness thresholds

Results of scenario analysis

Table 16: Strategies included in all scenario analysis

Strategy classification	Testing strategies by age				
	age 0-9	age 10-17	age 18-39	age 40-59	age 60+
Usual protocol/ best yield no misdiagnosis	N5_H_L_T0	N5_H_L_T0	N5_H_L_T0	N5_H_L_T0	N5_H_L_T0
Best yield with misdiagnosis	N5_H_L_T1	N5_H_L_T1	N5_H_L_T1	N5_H_L_T1	N5_H_L_T1
Base-case cost-effective at the £15,000/QALY threshold	N3_H5_L3_T1	N3_H5_L3_T1	N3_H6_L3_T1	N2_H2_L_T1	N3_H6_L2_T1
Base-case cost-effective at the £20,000/QALY threshold	N3_H5_L3_T1	N3_H5_L2_T1	N3_H6_L3_T1	N2_H2_L_T1	N3_H5_L1_T1
Base-case harmonised Cost-effective at the £15,000/QALY threshold	N3_H6_L3_T1	N3_H6_L3_T1	N3_H6_L3_T1	N3_H6_L3_T1	N3_H6_L3_T1
Base-case harmonised Cost-effective at the £20,000/QALY threshold	N3_H6_L2_T1	N3_H6_L2_T1	N3_H6_L2_T1	N3_H6_L2_T1	N3_H6_L2_T1

Testing strategies starting with N3 are strategies where relatives who are not on LLT are tested for their LDL-C, with relatives whose LDL-C ≥ higher cut-off are assumed to have FH, relatives with LDL-C between the higher and the lower cut-off are genetically tested, and relatives with LDL-C < lower cut-off are assumed not to have FH.

Strategies starting with N2 are strategies where relatives who are not on LLT are tested for their LDL-C, with relatives whose LDL-C ≥ higher cut-off are genetically tested, and relatives with LDL-C < higher cut-off are assumed not to have FH.

The number next to the letter "H" represents the higher cut-off for LDL-C.

The number next to the letter "L" represents the lower cut-off for LDL-C, where applicable.

Strategies terminating in T1 assume that relatives who are on LLT at the time of the cascade have FH without further testing.

QALY: quality-adjusted life year.

Table 17: Strategies specific to scenario analysis

Cost-effectiveness threshold (K) and Prevalence (P)	Scenario	Testing strategies by age				
		age 0-9	age 10-17	age 18-39	age 40-59	age 60+
K=£15,000/QALY; P=0.5	Using PASS Wales data to inform the proportion of FH relatives with no prior CV history on LLT.	N3_H5_L3_T1	N3_H5_L3_T1	N3_H6_L3_T1	N2_H2_L_T1	N3_H6_L2_T1
K=£15,000/QALY; P=0.25		N3_H5_L3_T1	N3_H5_L3_T1	N2_H3_L_T1	N2_H3_L_T1	N3_H6_L3_T1
K=£20,000/QALY; P=0.5		N3_H5_L3_T1	N3_H5_L2_T1	N3_H6_L3_T1	N5_H_L_T1	N5_H_L_T1
K=£20,000/QALY; P=0.25		N3_H5_L3_T1	N3_H5_L3_T1	N2_H3_L_T1	N2_H3_L_T1	N5_H_L_T1
K=£15,000/QALY; P=0.5	Using general population data to inform the proportion of FH relatives with no prior CV history on LLT.	N3_H5_L3_T0	N3_H5_L3_T0	N3_H5_L3_T1	N3_H6_L2_T1	N3_H5_L1_T1
K=£15,000/QALY; P=0.25		N3_H5_L3_T0	N3_H5_L3_T0	N3_H6_L3_T1	N2_H3_L_T0	N3_H6_L2_T0
K=£20,000/QALY; P=0.5		N3_H5_L3_T0	N3_H5_L2_T0	N3_H5_L2_T1	N3_H6_L2_T1	N3_H5_L1_T1
K=£20,000/QALY; P=0.25		N3_H5_L3_T0	N3_H5_L3_T0	N3_H6_L3_T1	N2_H2_L_T0	N5_H_L_T0
K=£15,000/QALY; P=0.5	The genetic test is conducted on a saliva swab taken by the relative and sent to the FH service by post.	N3_H5_L3_T1	N3_H4_L3_T1	N3_H5_L3_T1	N3_H6_L2_T1	N3_H5_L1_T1
K=£15,000/QALY; P=0.25		N3_H5_L3_T1	N3_H5_L3_T1	N3_H6_L3_T1	N2_H3_L_T1	N3_H6_L2_T1
K=£20,000/QALY; P=0.5		N3_H5_L3_T1	N3_H4_L2_T1	N3_H5_L3_T1	N3_H6_L2_T1	N3_H5_L1_T1
K=£20,000/QALY; P=0.25		N3_H5_L3_T1	N3_H5_L3_T1	N3_H6_L3_T1	N2_H2_L_T1	N5_H_L_T1
K=£15,000/QALY; P=0.5	In testing strategies where relatives have a cholesterol test and a genetic test, taking the second blood sample requires an additional nurse appointment.	N3_H5_L3_T1	N3_H4_L3_T1	N3_H5_L3_T1	N5_H_L_T1	N3_H5_L1_T1
K=£15,000/QALY; P=0.25		N3_H5_L3_T1	N3_H5_L3_T1	N3_H6_L3_T1	N2_H3_L_T1	N5_H_L_T1
K=£20,000/QALY; P=0.5		N3_H5_L3_T1	N3_H4_L2_T1	N3_H5_L3_T1	N5_H_L_T1	N3_H5_L1_T1
K=£20,000/QALY; P=0.25		N3_H5_L3_T1	N3_H5_L3_T1	N3_H6_L3_T1	N5_H_L_T1	N5_H_L_T1
K=£15,000/QALY; P=0.5	Non-FH relatives at high CV risk not on LLT and who are misdiagnosed with FH benefit from treatment.	N3_H5_L3_T1	N3_H5_L3_T1	N3_H5_L3_T1	N3_H5_L2_T1	N1_H1_L_T1
K=£15,000/QALY; P=0.25		N3_H5_L3_T1	N3_H5_L3_T1	N3_H6_L3_T1	N2_H3_L_T1	N1_H1_L_T1
K=£20,000/QALY; P=0.5		N3_H5_L3_T1	N3_H5_L2_T1	N3_H5_L2_T1	N3_H5_L2_T1	N1_H1_L_T1
K=£20,000/QALY; P=0.25		N3_H5_L3_T1	N3_H5_L3_T1	N3_H6_L3_T1	N3_H6_L2_T1	N1_H1_L_T1
K=£15,000/QALY; P=0.5	FH relatives on are on LLT have their LDLC reduced by 50% in line with the NICE CG71 [6].	N3_H5_L3_T1	N3_H5_L2_T1	N3_H5_L3_T1	N3_H6_L2_T1	N3_H5_L1_T1
K=£15,000/QALY; P=0.25		N3_H5_L3_T1	N3_H5_L3_T1	N3_H6_L3_T1	N2_H2_L_T1	N5_H_L_T1
K=£20,000/QALY; P=0.5		N3_H5_L2_T1	N3_H5_L2_T1	N3_H5_L2_T1	N5_H_L_T1	N3_H5_L1_T1
K=£20,000/QALY; P=0.25		N3_H5_L3_T1	N3_H5_L2_T1	N3_H6_L3_T1	N5_H_L_T1	N5_H_L_T1
K=£15,000/QALY; P=0.5	FH relatives who are diagnosed have their LDLC	N3_H5_L3_T1	N3_H5_L2_T1	N3_H5_L3_T1	N3_H6_L2_T1	N3_H5_L1_T1

Cost-effectiveness threshold (K) and Prevalence (P)	Scenario	Testing strategies by age				
		age 0-9	age 10-17	age 18-39	age 40-59	age 60+
K=£15,000/QALY; P=0.25	reduced by 50% irrespective if they are already on LLT [6], whereas FH relatives who are on LLT but who are not diagnosed have the LDLC reduction observed post-LLT in the CPRD cohort.	N3_H5_L3_T1	N3_H5_L3_T1	N3_H6_L3_T1	N2_H2_L_T1	N5_H_L_T1
K=£20,000/QALY; P=0.5		N3_H5_L2_T1	N3_H5_L2_T1	N3_H5_L2_T1	N5_H_L_T1	N3_H5_L1_T1
K=£20,000/QALY; P=0.25		N3_H5_L3_T1	N3_H5_L2_T1	N3_H6_L3_T1	N5_H_L_T1	N5_H_L_T1
K=£15,000/QALY; P=0.5	FH relatives on are on LLT have their LDLC reduced to the EAS targets [7].	N3_H5_L3_T1	N3_H5_L3_T1	N3_H5_L3_T1	N3_H6_L2_T1	N3_H5_L2_T1
K=£15,000/QALY; P=0.25		N3_H5_L3_T1	N3_H5_L3_T1	N3_H6_L3_T1	N2_H3_L_T1	N3_H6_L2_T1
K=£20,000/QALY; P=0.5		N3_H5_L3_T1	N3_H5_L3_T1	N3_H5_L3_T1	N3_H6_L2_T1	N3_H5_L2_T1
K=£20,000/QALY; P=0.25		N3_H5_L3_T1	N3_H5_L3_T1	N3_H6_L3_T1	N2_H3_L_T1	N3_H6_L2_T1
K=£15,000/QALY; P=0.5	The extrapolation of CV risk over time was based on the exponential survival model.	N3_H5_L2_T1	N3_H5_L2_T1	N3_H5_L2_T1	N5_H_L_T1	N3_H5_L1_T1
K=£15,000/QALY; P=0.25		N3_H5_L3_T1	N3_H5_L2_T1	N3_H6_L3_T1	N2_H2_L_T1	N5_H_L_T1
K=£20,000/QALY; P=0.5		N3_H5_L2_T1	N3_H5_L2_T1	N3_H5_L2_T1	N5_H_L_T1	N3_H5_L1_T1
K=£20,000/QALY; P=0.25		N3_H5_L2_T1	N3_H5_L2_T1	N3_H6_L2_T1	N5_H_L_T1	N5_H_L_T1
K=£15,000/QALY; P=0.5	The effect of LDLC on CV risk is constant over time and corresponds to the effect observed in the CTTC meta-analyses [10].	N1_H6_L_T1	N1_H5_L_T1	N3_H5_L4_T1	N3_H6_L3_T1	N3_H5_L2_T1
K=£15,000/QALY; P=0.25		N0_H_L_T	N1_H5_L_T1	N3_H6_L4_T1	N2_H3_L_T1	N3_H6_L2_T1
K=£20,000/QALY; P=0.5		N1_H5_L_T1	N3_H5_L4_T1	N3_H5_L3_T1	N3_H6_L2_T1	N3_H5_L1_T1
K=£20,000/QALY; P=0.25		N1_H5_L_T1	N3_H5_L4_T1	N3_H6_L3_T1	N2_H3_L_T1	N5_H_L_T1
K=£15,000/QALY; P=0.5	CV risk increases over time with age, as inferred using the standardised mortality ratios obtained comparing FH patients to the general population [11].	N3_H5_L3_T1	N3_H5_L3_T1	N3_H5_L2_T1	N5_H_L_T1	N3_H5_L1_T1
K=£15,000/QALY; P=0.25		N3_H5_L3_T1	N3_H5_L3_T1	N3_H6_L2_T1	N5_H_L_T1	N5_H_L_T1
K=£20,000/QALY; P=0.5		N3_H5_L3_T1	N3_H5_L2_T1	N3_H5_L2_T1	N5_H_L_T1	N4_H5_L_T1
K=£20,000/QALY; P=0.25		N3_H5_L3_T1	N3_H5_L3_T1	N3_H6_L2_T1	N5_H_L_T1	N5_H_L_T1
K=£15,000/QALY; P=0.5	Assuming low costs of monitoring patients with FH.	N3_H4_L3_T1	N3_H4_L2_T1	N3_H5_L3_T1	N3_H6_L2_T1	N3_H4_L1_T1
K=£15,000/QALY; P=0.25		N3_H5_L3_T1	N3_H5_L3_T1	N3_H6_L3_T1	N2_H3_L_T1	N3_H5_L2_T1
K=£20,000/QALY; P=0.5		N3_H4_L2_T1	N3_H4_L2_T1	N3_H5_L2_T1	N3_H6_L2_T1	N3_H4_L1_T1
K=£20,000/QALY; P=0.25		N3_H5_L3_T1	N3_H5_L2_T1	N3_H6_L3_T1	N2_H2_L_T1	N3_H5_L1_T1
K=£15,000/QALY; P=0.5	Assuming high costs of monitoring patients with FH.	N3_H5_L3_T1	N3_H5_L3_T1	N3_H6_L3_T1	N3_H6_L2_T1	N3_H5_L2_T0
K=£15,000/QALY; P=0.25		N3_H5_L3_T1	N3_H5_L3_T1	N3_H6_L3_T1	N2_H3_L_T0	N3_H6_L2_T0
K=£20,000/QALY; P=0.5		N3_H5_L3_T1	N3_H5_L3_T1	N3_H6_L3_T1	N3_H6_L2_T1	N3_H5_L1_T0
K=£20,000/QALY; P=0.25		N3_H5_L3_T1	N3_H5_L3_T1	N3_H6_L3_T1	N2_H3_L_T0	N5_H_L_T0

AWDLCN: Age-adjusted Welsh-modified Dutch Lipid Clinic Network criteria; CPRD: Clinical Practice Research Datalink; CTTC: Cholesterol Treatment Trialists Collaboration; CV: Cardiovascular; EAS: European Atherosclerosis Society; FH: Familial Hypercholesterolaemia; LDLC: Low-Density Lipoprotein Cholesterol; LLT: Lipid Lowering Treatment; FH: Monogenic Familial Hypercholesterolaemia; VUS: Variant of Unknown Significance; WDLCN: Welsh-modified Dutch Lipid Clinic Network criteria.

Table 18: Scenarios where cost-effective strategy did not change at the cost-effectiveness threshold of £15,000/QALY and £20,000/QALY

Scenario
Using the AWDLCN to select indexes, informed by PASS Wales.
Using Simon Broome criteria to select indexes, informed by PASS Wessex.
Out-of-area relatives are cascaded, with their numbers informed by PASS Wales.
Out-of-area relatives are cascaded, with their numbers informed by PASS Wessex.
Assuming that the VUS not yet reclassified are not FH.
Indexes with VUS are selected to the cascade and their affected relatives tested and managed as if they had FH.
The prevalence of FH is estimated from the PASS Welsh data.
The prevalence of FH is estimated from the PASS Wessex data.
The proportion of FH relatives with no prior CV history on LLT obtained from general population data.
The genetic test is conducted on a saliva swab taken by the relative and sent to the FH service by post.
Assuming low costs of monitoring patients with FH.

Table 19: Scenarios where the cost-effective strategy changed

Scenario	Cost-effective at	Difference in net monetary benefit (£)
The proportion of FH relatives with no prior CV history on LLT obtained from PASS Wales.	£15,000 /QALY	-1
	£20,000 /QALY	0
In testing strategies where relatives have a cholesterol test and a genetic test, taking the second blood sample requires an additional nurse appointment.	£15,000 /QALY	-2
	£20,000 /QALY	0
Non-FH relatives at high CV risk not on LLT and who are misdiagnosed with FH benefit from treatment.	£15,000 /QALY	-130
	£20,000 /QALY	-174
FH relatives on are on LLT have their LDLC reduced by 50% in line with the NICE CG71 [6].	£15,000 /QALY	0
	£20,000 /QALY	-2
FH relatives who are diagnosed have their LDLC reduced by 50% irrespective if they are already on LLT [6], whereas FH relatives who are on LLT but who are not diagnosed have the LDLC reduction observed post-LLT in the CPRD cohort.	£15,000 /QALY	0
	£20,000 /QALY	-2
FH relatives on are on LLT have their LDLC reduced to the EAS targets [7].	£15,000 /QALY	-2
	£20,000 /QALY	-6
The extrapolation of CV risk over time was based on the exponential survival model.	£15,000 /QALY	-17
	£20,000 /QALY	-23
The effect of LDLC on CV risk is constant over time and corresponds to the effect observed in the CTTC meta-analyses [10].	£15,000 /QALY	-100
	£20,000 /QALY	-71
CV risk increases over time with age, as inferred using the standardised mortality ratios obtained comparing FH patients to the general population [11]..	£15,000 /QALY	-12
	£20,000 /QALY	-25
Assuming high costs of monitoring patients with FH.	£15,000 /QALY	-8
	£20,000 /QALY	-10

AWDLCN: Age-adjusted Welsh-modified Dutch Lipid Clinic Network criteria; CPRD: Clinical Practice Research Datalink; CTTC: Cholesterol Treatment Trialists Collaboration; CV: Cardiovascular; EAS: European Atherosclerosis Society; FH: Familial Hypercholesterolaemia; LDLC: Low-Density Lipoprotein Cholesterol; LLT: Lipid Lowering Treatment; FH: Monogenic Familial Hypercholesterolaemia; NA: Not applicable; VUS: Variant of Unknown Significance; WDLCN: Welsh-modified Dutch Lipid Clinic Network criteria.

Table 20: Protocols with the highest net health gain in the scenario analysis

Threshold, /QALY	WDLCN cut-off	Type of cascade	Method of contact	Testing strategies by age				
				age 0-9	age 10-17	age 18-39	age 40-59	age 60+
Base-case								
£15,000	6	concomitant	direct	N3_H5_L3_T1	N3_H5_L3_T1	N3_H6_L3_T1	N2_H2_L_T1	N3_H6_L2_T1
£20,000					N3_H5_L2_T1			N3_H5_L1_T1
The proportion of FH relatives with no prior CV history on LLT obtained from PASS Wales.								
£15,000	=base-case						N2_H3_L_T1	N5_H_L_T1
£20,000	=base-case					N3_H6_L3_T1	N5_H_L_T1	N5_H_L_T1
In testing strategies where relatives have a cholesterol test and a genetic test, taking the second blood sample requires an additional nurse appointment.								
£15,000	=base-case						N5_H_L_T1	N5_H_L_T1
£20,000	=base-case				N3_H5_L3_T1	=base-case	N5_H_L_T1	N5_H_L_T1
Non-FH relatives at high CV risk not on LLT and who are misdiagnosed with FH benefit from treatment								
£15,000	=base-case						N3_H6_L2_T1	N1_H1_L_T1
£20,000	=base-case				N3_H5_L3_T1	N3_H5_L3_T1	N3_H5_L2_T1	N1_H1_L_T1
FH relatives on are on LLT have their LDLC reduced by 50% in line with the NICE CG71 [6].								
£15,000	=base-case				N3_H5_L2_T1	N3_H6_L3_T1	N5_H_L_T1	N5_H_L_T1
£20,000	=base-case			N3_H5_L2_T1	=base-case	N3_H5_L2_T1	N5_H_L_T1	=base-case
FH relatives who are diagnosed have their LDLC reduced by 50% irrespective if they are already on LLT [6], whereas FH relatives who are on LLT but who are not diagnosed have the LDLC reduction observed post-LLT in the CPRD cohort								
£15,000	=base-case				N3_H5_L2_T1	=base-case	N5_H_L_T1	N5_H_L_T1
£20,000	=base-case			N3_H5_L2_T1	=base-case	N3_H5_L2_T1	N5_H_L_T1	=base-case
FH relatives on are on LLT have their LDLC reduced to the EAS targets [7].								
£15,000	=base-case						N2_H3_L_T1	=base-case
£20,000	=base-case				N3_H5_L3_T1	=base-case		N3_H6_L2_T1

Threshold, /QALY	WDLCN cut-off	Type of cascade	Method of contact	Testing strategies by age				
				age 0-9	age 10-17	age 18-39	age 40-59	age 60+
The extrapolation of CV risk over time was based on the exponential survival model.								
£15,000	=base-case			N3_H5_L2_T1	N3_H5_L2_T1	N3_H6_L2_T1	N5_H_L_T1	N5_H_L_T1
£20,000	=base-case			N3_H5_L2_T1	=base-case	N3_H6_L2_T1	N5_H_L_T1	N5_H_L_T1
The effect of LDLC on CV risk is constant over time and corresponds to the effect observed in the CTTC meta-analyses [10].								
£15,000	=base-case			N1_H6_L_T0	N1_H5_L_T1	N3_H6_L4_T1	N2_H3_L_T1	=base-case
£20,000	=base-case			N1_H5_L_T1	N3_H5_L4_T1	=base-case	N2_H3_L_T1	N5_H_L_T1
CV risk increases over time with age, as inferred using the standardised mortality ratios obtained comparing FH patients to the general population [11].								
£15,000	=base-case					N3_H6_L2_T1	N5_H_L_T1	N5_H_L_T1
£20,000	=base-case				N3_H5_L3_T1	N3_H6_L2_T1	N5_H_L_T1	N5_H_L_T1
Assuming high costs of monitoring patients with FH.								
£15,000	=base-case					=base-case	N2_H3_L_T0	N3_H6_L2_T0
£20,000	=base-case				N3_H5_L3_T1	=base-case	N2_H3_L_T0	N3_H6_L2_T0

Testing strategies starting with N3 are strategies where relatives who are not on LLT are tested for their LDL-C, with relatives whose LDL-C ≥ higher cut-off are assumed to have FH, relatives with LDL-C between the higher and the lower cut-off are genetically tested, and relatives with LDL-C < lower cut-off are assumed not to have FH.

Strategies starting with N2 are strategies where relatives who are not on LLT are tested for their LDL-C, with relatives whose LDL-C ≥ higher cut-off are genetically tested, and relatives with LDL-C < higher cut-off are assumed not to have FH.

The number next to the letter "H" represents the higher cut-off for LDL-C.

The number next to the letter "L" represents the lower cut-off for LDL-C, where applicable.

Strategies terminating in T1 assume that relatives who are on LLT at the time of the cascade have FH without further testing.

QALYs: Quality Adjusted Life Years; WDLCN: Welsh-modified Dutch Lipid Clinic Network.

6. Long-term outcomes of relatives who do not have monogenic familial hypercholesterolaemia (FH)

Cascade testing can affect the long-term outcomes and costs of relatives who do not have FH, henceforth referred to as non-FH relatives if they are misdiagnosed with FH and managed accordingly (i.e. false positives). FH misdiagnosis may result in better health outcomes if non-FH relatives are at high risk of cardiovascular disease (CVD) but are not on LLT at the time of the cascade. However, it would involve greater costs than if relatives were treated in the primary care setting in line with the NICE guideline for lipid modification in the general population [22]. FH misdiagnosis is not expected to improve health outcomes if non-FH relatives are not at high risk of cardiovascular disease, although it will increase costs to the NHS. Additionally, FH misdiagnosis may reduce health outcomes due to the adverse effects of LLT, or if the knowledge of having the condition has a direct impact on relatives.

The implication is that the cost-effectiveness analysis of alternative cascade protocols needs to capture the long-term outcomes and costs of non-FH under two scenarios: (i) misdiagnosis of FH and subsequent treatment; and (ii) correct diagnosis as not having FH and no change in treatment, that is, continuation of LLT for CVD prevention or continuation of no treatment.

Methods

We estimated the long-term QALYs and NHS costs of non-FH relatives at a 2019 price base, and discounted future costs and outcomes at 3.5% [23] . We adapted the cost-effectiveness model developed and kindly shared by the National Guideline Centre to inform NICE CG181, henceforth referred to the NICE model [24] .

Population and subgroups

We stratified non-FH relatives into two subgroups: relatives who are at high CV risk, in whom the NICE CG181 recommends LLT [22], and relatives who are at low CV risk. Following the NICE CG181 [22], we considered that non-FH relatives who have a QRISK2 score of 10% or more are at high CV risk and are eligible for LLT, with the QRISK2 score being interpreted as 10-year CV risk [25]. We assumed that non-FH relatives aged 39 years and younger were at low CV risk.

So that we could link the results to the model for the cost-effectiveness analysis of cascade protocols, we further stratified the non-FH relatives into the age, sex, CV history, and whether on LLT at the time of the cascade. We excluded pre-treatment low density lipoprotein cholesterol (PT-LDLC) as a stratifying characteristic because the NICE model does not consider it, and because we were unable to find evidence from the literature on QRISK2 scores by LDL-C. This is unlikely to affect the results given the relatively small effect of cholesterol in QRISK2 score compared to the effect of age and sex (hazard ratio = 1.17 (95% CI 1.16 to 1.18) for high-density lipoprotein cholesterol to total cholesterol ratio vs HR=1.66 (95% CI1.65 to 1.68) for 10% increase in age) [25].

Decision options

Following the outcomes required to inform the cost-effectiveness model on cascade protocols, we modelled three decision options: (i) misdiagnosis as FH and subsequent treatment, and continuation of previous management, either (ii) continuation of LLT for CVD prevention as part of the usual pathway for patients at high CV risk, or (iii) continuation of no treatment.

Modelling approach

Our modelling approach depended on the non-FH subgroup: at high risk or at low risk of CVD. For the long-term outcomes of non-FH relatives at low CV risk, we developed a simple “alive-dead” model, informed by the general population mortality risk and general population health-related quality of life [26,27] to calculate quality-adjusted life years (QALYs) and cost of treatment, monitoring

and adverse effects. It did not include costs or health impact of future CV events. We used this model for the subgroups aged < 18 years at the time of the cascade to lifetime and for subgroups aged < 39 years at the time of the cascade up to 40 years of age if they were at high CV risk from this age, or to lifetime if they remained at low CV risk.

For the long-term outcomes of non-FH relatives at high CV risk, we used NICE model [24]. This model was developed and validated to estimate the cost-effectiveness of LLT in the general population at high CV risk. It is a Markov model with annual cycles with health states for prior to any CV event (the "well" state), stable angina, unstable angina, myocardial infarction, stroke, transient ischaemic attack, heart failure and peripheral arterial disease. For primary prevention of CVD, all patients enter the model in the 'well state' and are at risk of a CV event. After a CV event, patients are apportioned over the various types of CV events represented in the health states and are a risk of subsequent events. For secondary prevention, patients enter the model distributed across the post-CV event health states, representing their prior CV history. LLT reduces the CV event risk and the risk of death independently of PT-LDLC as estimated in the systematic review and meta-analysis conducted for the NICE CG181 [22].

Key assumptions

We assumed that misdiagnosis increases costs via monitoring, LLT acquisition costs and adverse effects in both the high and low CV risk groups; however, it does not affect health outcomes compared to the existing care (either continuation of LLT for CVD prevention as part of the usual pathway for patients at high CV risk, or continuation of no treatment). This was a simplification given that the evaluation of strategies to improve uptake of LLT of non-FH relatives at high CV risk was outside the scope of the project. Without this assumption, misdiagnosis would be cost-effective in some non-FH relatives at high CV risk who were not on LLT at the time of the cascade, given the risk reduction of LLT and its low cost, and the less than optimal implementation of the NICE CG181 guideline [2,22,28,29].

We assumed that patients do not start LLT over time, given the low statin initiation rate over time (e.g. 0.8% to 4% per patient-year spent eligible for a CV risk assessment [30].

The feedback of our Stakeholder Group was that the probability that the contact with the FH service leads to LLT initiation as part of the pathway for CVD prevention for the general population was small; hence we did not include it in our analysis.

Model inputs

For non-FH relatives at high risk of CVD, we used the NICE model with the original inputs [24], apart from some updates to the costs and using estimates of 10-year CV risk to reflect the average risk by age and sex in the general population.

Effect of FH misdiagnosis and of LLT in non-FH relatives at high CV risk

We chose medium-intensity statins to represent the effect of LLT, given the average reduction of 31% observed in the CPRD cohort post-FH diagnosis, which is similar to the expected effect of medium-intensity statins, and our assumption that this represents the effect of FH diagnosis in clinical practice in the cost-effectiveness model on the long-term outcomes and costs of patients with FH.

CV risk

Table 21 shows the model inputs related to CV risk and LLT. For the proportion of non-FH relatives at high CV risk, we used the study by Ueda et al [28], which estimated QRISK2 scores using Health Survey for England 2011 data, a representative national survey. We calculated the average QRISK2 for those at high CV risk (QRISK2>=10%) from the results of the analysis of Ueda et al [29], which also used Health Survey for England data for 2009-2013 on English adults aged 40-75 without prior CVD. We assumed that non-FH relatives at low CV risk are not on LLT as part of the general population

pathway. Therefore, all non-FH relatives who are on LLT at the time of the cascade are at high CV risk.

Table 21: Model inputs related to CV risk and LLT

Age, years	Sex	Value	Source
High CV risk (QRISK2 >= 10%)			
40-59	Male	33%	Ueda et al [28], read from Figure 4 Age 40-59 corresponds to age 45-59 in Ueda et al Age 60+ corresponds to age 60-75 in Ueda et al
	Female	9%	
60+	Male	95%	
	Female	65%	
Average QRISK2 with those at high CV risk			
40-59	Both	17%	Ueda et al [29], calculated from Table 2, assuming that number of events represents number of people who had events.
60+		22%	
Proportion of patients who are on LLT and who are at high CV risk			
40-59	Male	14%	Ueda et al [28], read from Figure 4 Age 40-59 corresponds to age 45-59 in Ueda et al Age 60+ corresponds to age 60-75 in Ueda et al
	Female	8%	
60+	Male	30%	
	Female	19%	
CV: Cardiovascular; LLT: Lipid Lowering Treatment.			

Costs

We updated all unit costs to 2019 in line with the cost-effectiveness model on the long-term outcomes and costs of patients with FH, used the drug acquisition and monitoring costs calculated for the FH model to inform the costs related to FH diagnosis, and used the unit cost of atorvastatin 10 mg to represent the acquisition costs of LLT for prevention of CVD in the general population [31], because it was the cheapest medium-intensity statin.

Scenario analysis

We ran a scenario analysis to the costs of monitoring patients if they are misdiagnosed with FH (high or low monitoring costs), in line with the scenario analysis of the cost-effectiveness model on the long-term outcomes and costs of patients with FH; and a scenario analysis assuming that FH misdiagnosis improves the health outcomes of non-FH relatives at high CV risk who are not on LLT at the time of the cascade.

Analytical methods

We obtained results for subgroups of non-FH relatives in terms of age, sex, prior CV history, and whether on LLT at the time of the cascade, by treatment scenario: no treatment, treatment for CVD prevention, and FH misdiagnosis and subsequent treatment. Results are probabilistic over 1000 simulations in the base-case, and deterministic in the scenarios.

Validation

Given that the small extent of the adaptations to the NICE model and the simplicity of the “alive-death” model, we conducted a summary validation of their implementation. The validation consisted of the verification of the new formulas and new VBA code by the main modeller (RF), extreme value testing of the “alive-dead” model, and validation of the predictions with the wider economic team.

Results

Table 22: Base-case results of health outcomes and costs of non-FH relatives

Relatives' subgroups				FH misdiagnosis		Treatment for prevention of CVD		No treatment	
Age entry	**Sex**	**CV history**	**On LLT?**	**QALYs**	**Costs**	**QALYs**	**Costs**	**QALYs**	**Costs**
age 0-9	male	No CVD	No LLT	25.24	£4,210	NA	NA	25.24	£0
age 0-9	female	No CVD	No LLT	24.82	£4,228	NA	NA	24.82	£0
age 10-17	male	No CVD	No LLT	24.04	£3,663	NA	NA	24.04	£0
age 10-17	female	No CVD	No LLT	23.74	£3,728	NA	NA	23.74	£0
age 18-39	male	No CVD	No LLT	22.59	£4,195	NA	NA	22.59	£2,301
age 18-39	female	No CVD	No LLT	21.66	£2,776	NA	NA	21.66	£574
age 40-59	male	No CVD	No LLT	15.25	£2,767	15.25	£1,352	15.25	£1,352
age 40-59	male	No CVD	On LLT	13.80	£6,277	13.80	£6,101	NA	NA
age 40-59	male	Prior CVD	No LLT	8.90	£13,326	8.90	£13,139	8.90	£13,139
age 40-59	male	Prior CVD	On LLT	8.88	£13,310	8.88	£13,115	NA	NA
age 40-59	female	No CVD	No LLT	15.96	£1,917	15.96	£64	15.96	£64
age 40-59	female	No CVD	On LLT	14.29	£5,998	14.29	£5,826	NA	NA
age 40-59	female	Prior CVD	No LLT	8.88	£11,025	8.88	£10,858	8.88	£10,858
age 40-59	female	Prior CVD	On LLT	8.88	£11,017	8.88	£10,843	NA	NA
age 60+	male	No CVD	No LLT	8.37	£4,054	8.37	£3,829	8.37	£3,829
age 60+	male	No CVD	On LLT	8.34	£4,271	8.34	£4,117	NA	NA
age 60+	male	Prior CVD	No LLT	5.22	£10,060	5.22	£9,896	5.22	£9,896
age 60+	male	Prior CVD	On LLT	5.22	£10,065	5.22	£9,886	NA	NA
age 60+	female	No CVD	No LLT	9.10	£3,118	9.10	£2,510	9.10	£2,510
age 60+	female	No CVD	On LLT	8.95	£4,563	8.95	£4,384	NA	NA
age 60+	female	Prior CVD	No LLT	5.43	£10,644	5.43	£10,470	5.43	£10,470
age 60+	female	Prior CVD	On LLT	5.43	£10,637	5.43	£10,457	NA	NA

CVD: Cardiovascular Disease; LLT: Lipid-lowering treatment; NA: Not Applicable; QALYs: Quality-Adjusted Life Years.

Table 23: Scenario results of health outcomes and costs of non-FH relatives assuming that non-FH relatives at high CV risk benefit from FH misdiagnosis

Relatives' subgroups				FH misdiagnosis		Treatment for prevention of CVD		No treatment	
Age entry	**Sex**	**CV history**	**On LLT?**	**QALYs**	**Costs**	**QALYs**	**Costs**	**QALYs**	**Costs**
age 0-9	male	No CVD	No LLT	25.24	£4,205	NA	NA	25.24	£0
age 0-9	female	No CVD	No LLT	24.82	£4,236	NA	NA	24.82	£0
age 10-17	male	No CVD	No LLT	24.04	£3,686	NA	NA	24.04	£0

age 10-17	female	No CVD	No LLT	23.74	£3,728	NA	NA	23.74	£0
age 18-39	male	No CVD	No LLT	22.59	£4,211	NA	NA	22.47	£2,296
age 18-39	female	No CVD	No LLT	21.66	£2,790	NA	NA	21.65	£572
age 40-59	male	No CVD	No LLT	15.26	£2,781	15.26	£1,355	15.14	£1,286
age 40-59	male	No CVD	On LLT	13.82	£6,304	13.82	£6,133	NA	NA
age 40-59	male	Prior CVD	No LLT	8.94	£13,413	8.94	£13,243	8.41	£11,526
age 40-59	male	Prior CVD	On LLT	8.94	£13,413	8.94	£13,243	NA	NA
age 40-59	female	No CVD	No LLT	15.96	£1,922	15.96	£64	15.95	£59
age 40-59	female	No CVD	On LLT	14.30	£6,027	14.30	£5,856	NA	NA
age 40-59	female	Prior CVD	No LLT	8.92	£11,083	8.92	£10,913	8.37	£9,324
age 40-59	female	Prior CVD	On LLT	8.92	£11,083	8.92	£10,913	NA	NA
age 60+	male	No CVD	No LLT	8.38	£4,079	8.38	£3,847	8.12	£3,503
age 60+	male	No CVD	On LLT	8.36	£4,308	8.36	£4,143	NA	NA
age 60+	male	Prior CVD	No LLT	5.39	£10,329	5.39	£10,165	5.02	£9,022
age 60+	male	Prior CVD	On LLT	5.39	£10,329	5.39	£10,165	NA	NA
age 60+	female	No CVD	No LLT	9.11	£3,132	9.11	£2,514	8.92	£2,279
age 60+	female	No CVD	On LLT	8.97	£4,592	8.97	£4,426	NA	NA
age 60+	female	Prior CVD	No LLT	5.56	£10,878	5.56	£10,713	5.17	£9,464
age 60+	female	Prior CVD	On LLT	5.56	£10,878	5.56	£10,713	NA	NA

CVD: Cardiovascular Disease; LLT: Lipid-lowering treatment; NA: Not Applicable; QALYs: Quality-Adjusted Life Years.

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