Supplementary Material

Cost-utility analysis of searching electronic health records and cascade testing to identify and diagnose familial hypercholesterolaemia in England and Wales

Contents

1 Detailed description of pathways for short term identification and diagnosis module

1.1 Strategy 1: No cascade testing and no case identification

This is effectively a 'do nothing' scenario so there are no short term costs associated with this strategy. Long term costs and health outcomes will accrue according to the long term module people enter at the end of the diagnostic pathway.

1. People with a current clinical diagnosis of FH: All receive treatment with statins, ezetimibe, or statins and ezetimibe, regardless of whether they have monogenic FH or polygenic hypercholesterolaemia. In this model polygenic hypercholesterolaemia is taken to mean people who have high cholesterol but in whom the monogenic mutation is not present. This group would include people who have elevated cholesterol for other reasons but their outcomes and treatment would not be appreciably different. They were therefore not modelled separately.
2. Relatives of people with a current clinical diagnosis of FH: Relatives with FH remain untreated and have a higher risk of myocardial infarction, angina and coronary heart disease. Relatives without FH (allocated as 'healthy' in the model) are not included in long term modelling because their numbers do not change between strategies.
3. People identified in a primary care database as requiring further investigation: A proportion of people with and without FH will already be on statins regardless of intervention and these people are assigned to the treated polygenic hypercholesterolaemia module or treated FH module according to. All other people remain untreated in this strategy.
4. Relatives of people identified in a primary care database who have FH: All relatives with FH remain untreated. Relatives without FH (allocated as 'healthy' in the model) are not included in long term modelling because their numbers do not change between strategies.
5. People identified in a secondary care database as requiring further investigation: All people with FH and polygenic hypercholesterolaemia are treated with high-intensity statins for secondary prevention due to their history of cardiovascular disease. Therefore, this subpopulation has no impact on incremental differences in long term costs and QALYs.
6. Relatives of people identified in a secondary care database who have FH: All relatives with FH remain untreated. Relatives without FH (allocated as 'healthy' in the model) are not included in long term modelling because their numbers do not change between strategies.

1.2 Strategy 2: Genetic cascade testing from monogenic FH index cases

1. People with a current clinical diagnosis of FH: Most of this subpopulation incur a cost to undergo a genetic test to determine their family mutation according to the take up rate of genetic testing for current index cases. A proportion will have a functional mutation in the LDLR, APOB, or PCSK9 gene. The remainder are assumed to have a polygenic cause of their hypercholesterolaemia. All people receive treatment with statins, ezetimibe or statins and ezetimibe regardless of the outcome of the genetic test in the base case.
2. Relatives of people with a current clinical diagnosis of FH: Relatives of current index cases found to have monogenic FH are contacted and offered genetic counselling and testing. Some of the relatives take up the offer. Some of the proportion (approx. 50% in the base case) that take up the offer will have the family mutation and receive appropriate

treatment. Relatives that do not have the mutation (noted as 'healthy' in the model) are not included in long term modelling as they remain constant between strategies. Genetic testing is assumed to have perfect diagnostic performance so there are no false positives or false negatives in this strategy. Relatives with FH who do not take up genetic testing remain untreated and have a higher risk of experiencing coronary heart disease. 'Healthy' relatives who do not take up genetic testing and do not have FH are not included in long term modelling because the overall number of healthy people does not change between strategies.

3. People identified in a primary care database as requiring further investigation: As per Strategy 1.
4. Relatives of people identified in a primary care database who have FH: As per Strategy 1.
5. People identified in a secondary care database as requiring further investigation: As per Strategy 1.
6. Relatives of people identified in a secondary care database who have FH: As per Strategy 1.

1.3 Strategy 3: Primary care case identification, clinical assessment using the Simon Broome criteria, and cascade testing of the relatives of newly identified index cases, in addition to cascade testing from currently diagnosed index cases

1. People with a current clinical diagnosis of FH: As per Strategy 2.
2. Relatives of people with a current clinical diagnosis of FH: As per Strategy 2.
3. People identified in a primary care database as requiring further investigation: Resources are required to set up informatics in GP surgeries and these costs are spread across people identified as requiring further investigation. Those identified by the database search have their medical records examined by a practice nurse and invited for clinical assessment using the Simon Broome criteria. Those patients that take up the invitation and are identified as having possible or definite FH during a clinical assessment with a nurse specialist are referred to a lipid clinic for genetic testing. In the base case, both possible and definite cases of FH are referred. In a sensitivity analysis, only definite FH is referred. Those identified as possible or definite FH by the clinical assessment either have monogenic FH (true positives) or not (false positives). False positives (before they are identified as such) undergo a genetic test, overturning their initial clinical diagnosis, and enter the long term module as 'treated polygenic' hypercholesterolaemia. So although they do not have FH, coming into contact with a healthcare professional means they moved from an untreated to treated state – they have high cholesterol but are not part of the portion of the population already on lipid modification. True positives undergo a genetic test which confirms their diagnosis of FH and they enter the 'treated FH' long term module. Out of the people that the Simon Broome criteria determines do not have possible or definite FH, some will actually have monogenic FH (false negatives) and the remainder will not (true negatives). False negatives enter the 'treated FH' module because, although the clinical assessment found (incorrectly) they did not have FH, they still have high cholesterol and have come into contact with health care, consistent with the assumption regarding false positives above. Following NICE CG181, these people would be prescribed a high-intensity statin. True negatives are assigned to the 'treated polygenic' long term module. People identified by the primary care database search as requiring further investigation but refuse the offer of clinical assessment are allocated to the 'untreated FH' or 'untreated polygenic' long term modules, except for the proportion of the population who are already on lipid modification treatment who are assigned to the

'treated FH' or 'treated polygenic' modules. The proportions of true positives, false negatives, false positives and true negatives are determined by the sensitivity and specificity of the Simon Broome criteria.

4. Relatives of people identified in a primary care database who have FH: Relatives of the new index cases with FH who took up clinical assessment and genetic testing are offered cascade testing and follow the same path as that specified for subpopulation 2 above. Whether they are offered cascade testing depends on the likelihood of potential new index cases being correctly identified as having FH. For example, the relatives of a person incorrectly diagnosed as not having FH by the clinical assessment tool (false negative) will not be offered cascade testing.
5. People identified in a secondary care database as requiring further investigation: As per Strategy 1.
6. Relatives of people identified in a secondary care database who have FH: As per Strategy 1.

1.4 Strategy 4: Primary care case identification, clinical assessment using the DLCN criteria, and cascade testing of the relatives of newly identified cases, in addition to cascade testing from currently diagnosed index cases.

As per Strategy 3 with the exception of using the DLCN criteria as the clinical assessment tool. In the base case referral to a lipid clinic for genetic testing occurs with scores greater than 5 (termed probable or definite in the DLCN criteria), increased to 8 or above in sensitivity analysis.

1.5 Strategy 5: Secondary care case identification, clinical assessment using the Simon Broome criteria, and cascade testing of the relatives of newly identified index cases, in addition to cascade testing from currently diagnosed index cases.

1. People with a current clinical diagnosis of FH: As per Strategy 2.
2. Relatives of people with a current clinical diagnosis of FH: As per Strategy 2.
3. People identified in a primary care database as requiring further investigation: As per Strategy 1.
4. Relatives of people identified in a primary care database who have FH: As per Strategy 1.
5. People identified in a secondary care database as requiring further investigation: People with early MI are invited to undergo further clinical assessment with the Simon Broome criteria. Those that take up the offer and are identified as having possible or definite FH are referred to a lipid clinic. Genetic testing confirms this diagnosis (true positive) or overturns it (false positive). Out of the people that the Simon Broome criteria determines do not have possible or definite FH, some will actually have FH (false negative) and the remainder will not (true negative). True positives are assigned to the 'treated FH' long term module. False positives, although the genetic test finds they do not have FH, still have high cholesterol and enter the 'treated polygenic' module. The proportion of people that do not take up the offer of clinical assessment still enter the 'treated FH' or 'treated polygenic' long term modules. The long term outcomes for this subpopulation do not change between strategies because they are treated with lipid modification regardless of diagnosis due to the need for secondary prevention following their myocardial infarction. What does change is the short term cost of searching the database, clinical assessment and genetic testing offset against the health benefits that accrue to their relatives (following take up and correct diagnosis) who otherwise would have remained undiagnosed and untreated.

6. Relatives of people identified in a secondary care database who have FH: As per relatives of people identified in primary care with FH.

1.6 Strategy 6: Secondary care case identification, clinical assessment using the DLCN criteria, and cascade testing of the relatives of newly identified index cases, in addition to cascade testing from currently diagnosed index cases.

This is the same as Strategy 5 apart from using the DLCN criteria as the clinical assessment tool.

1.7 Strategy 7: Primary care case identification, secondary care case identification, clinical assessment using the Simon Broome criteria, and cascade testing of the relatives of newly identified index cases, in addition to cascade testing from currently diagnosed index cases.

1. People with a current clinical diagnosis of FH: As per Strategy 2.
2. Relatives of people with a current clinical diagnosis of FH: As per Strategy 2.
3. People identified in a primary care database as requiring further investigation: As per Strategy 3.
4. Relatives of people identified in a primary care database who have FH: As per Strategy 3.
5. People identified in a secondary care database as requiring further investigation: As per Strategy 5.
6. Relatives of people identified in a secondary care database who have FH: As per Strategy 5.

1.8 Strategy 8: Primary care case identification, secondary care case identification, clinical assessment using the DLCN criteria, and cascade testing of the relatives of newly identified index cases, in addition to cascade testing from currently diagnosed index cases.

As per Strategy 7 but using the DLCN criteria for clinical assessment.

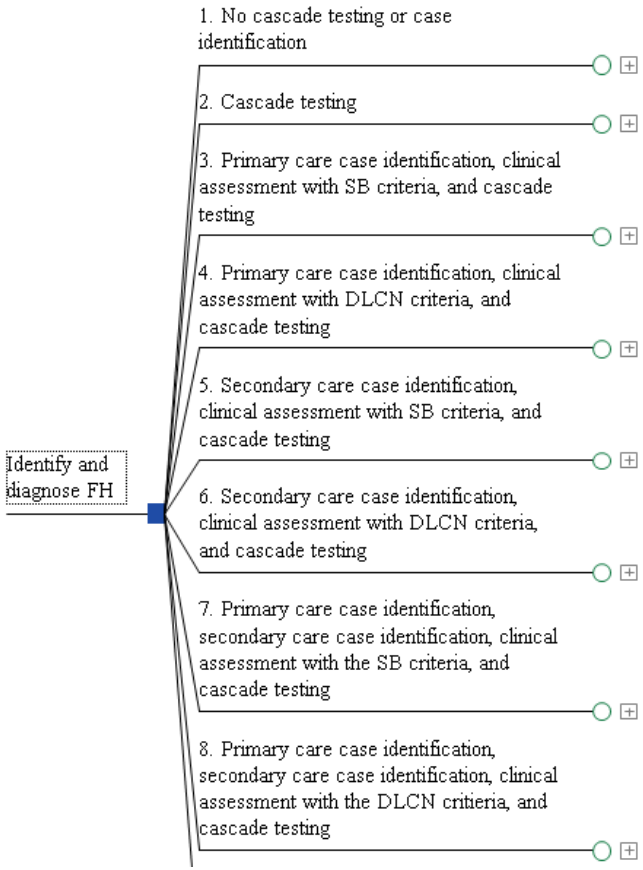
1.9 Strategy 9: Treat all people with high cholesterol in primary care with lipid modification regardless of FH status, no clinical assessment or genetic testing for FH, cascade testing from currently diagnosed index cases only.

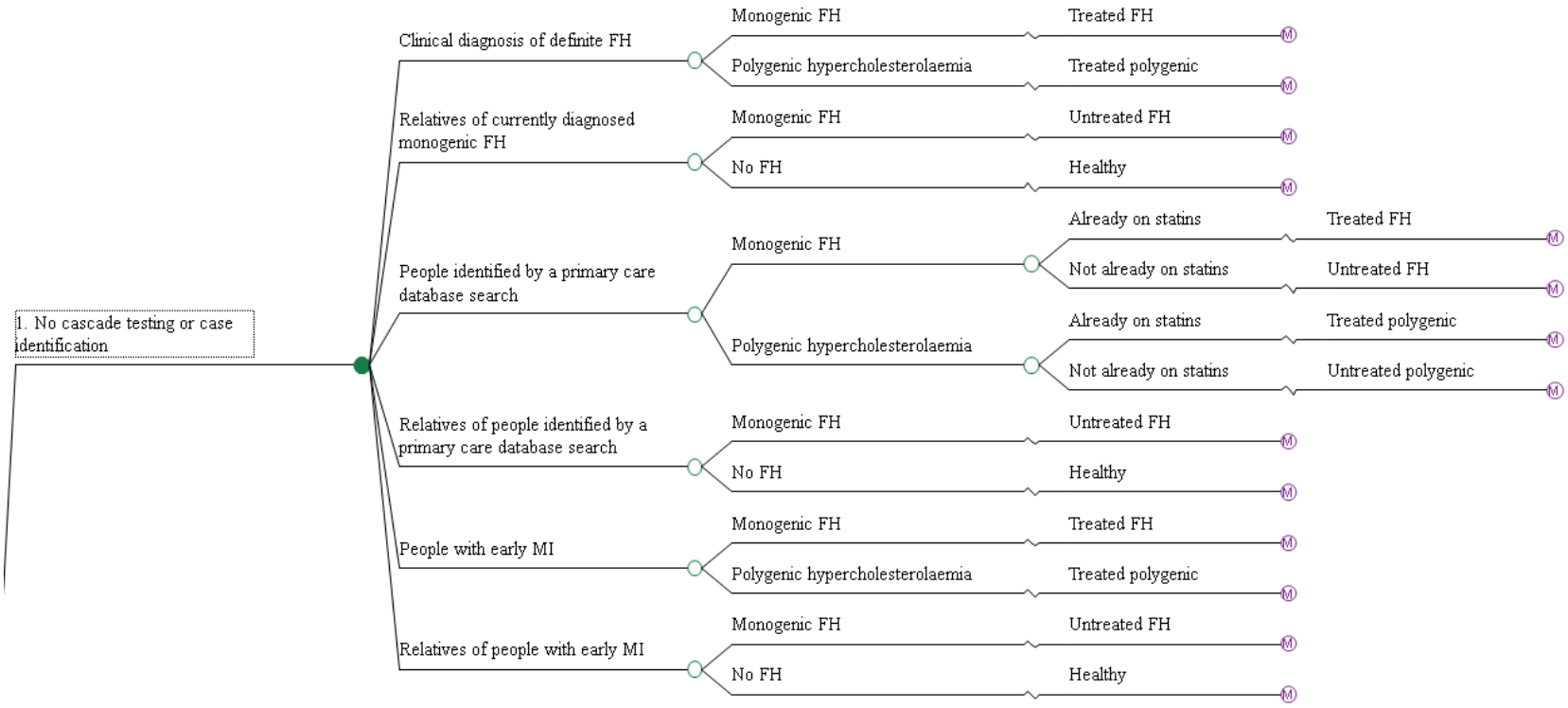
Much of the health benefit produced by case identification strategies was due to the polygenic population with high cholesterol being invited for further assessment and receiving appropriate treatment (assuming they took up the offer). The purpose of including this strategy was to investigate the incremental benefit of ensuring that all people with high cholesterol recorded in primary care databases were prescribed lipid modification treatment, regardless of FH status, compared with the closest representation of current practice, cascade testing from index cases with a current clinical diagnosis of FH only. This involves a decrease in costs otherwise associated with referral to a lipid clinic and subsequent genetic testing at the same time as retaining the health benefits for people with high cholesterol who were not already taking lipid modification and take up clinical assessment in primary care. However, the relatives of people who have FH do not accrue any health benefits because cascade testing is not initiated without diagnosing the potential new index cases with FH. It is questionable whether such a strategy would be implemented in practice but it

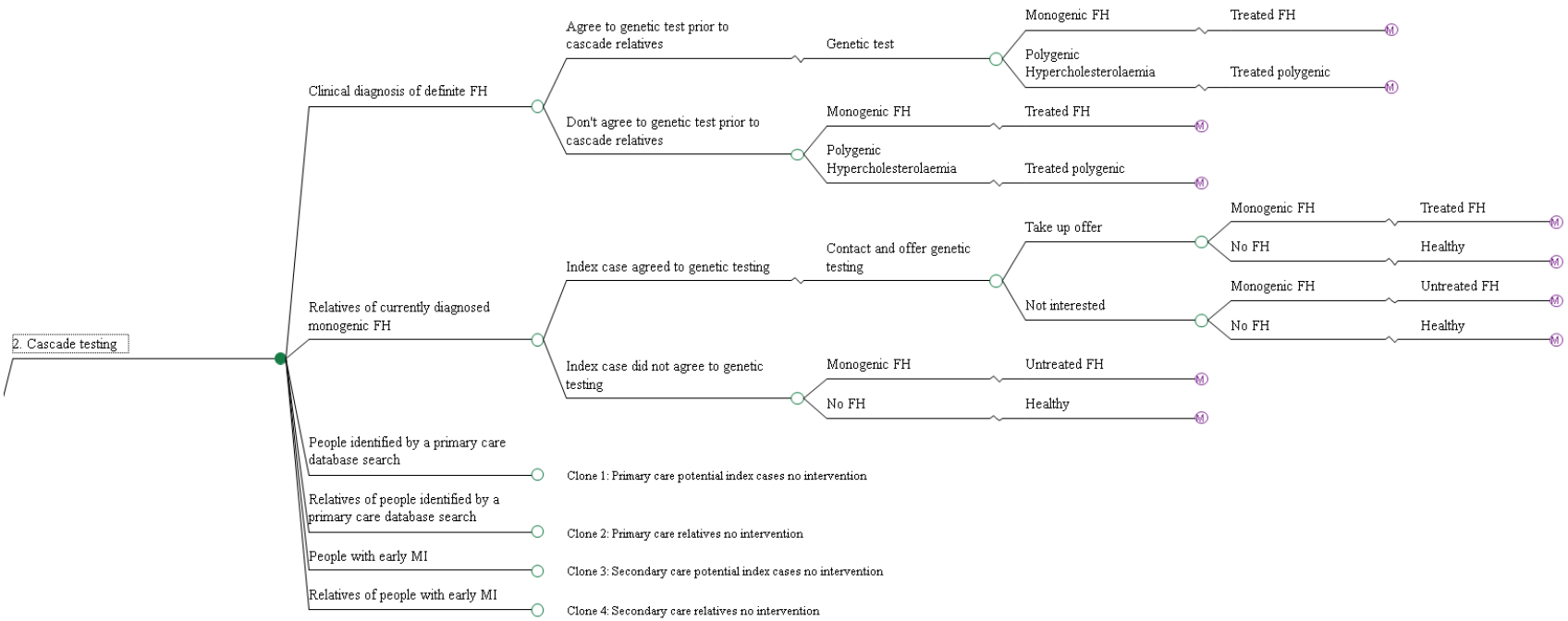
does provide further evidence that the resource impact of genetic testing to properly diagnose new index cases and cascade testing their relatives is cost effective in the event that strategies 3 to 8 are cost effective compared with strategy 9.

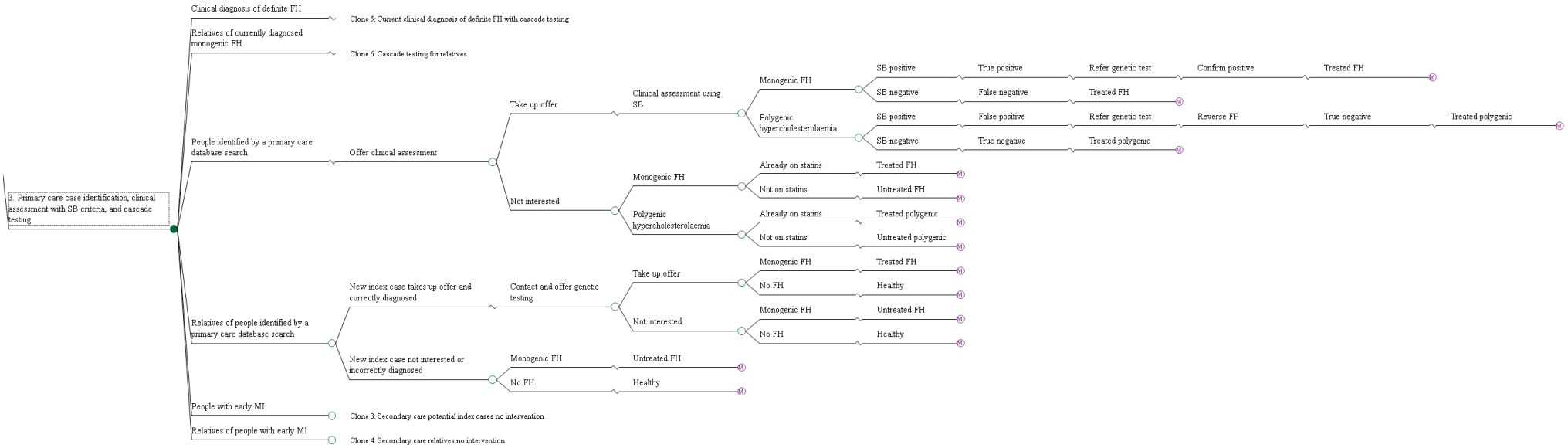
2 Structure of case identification and diagnosis module

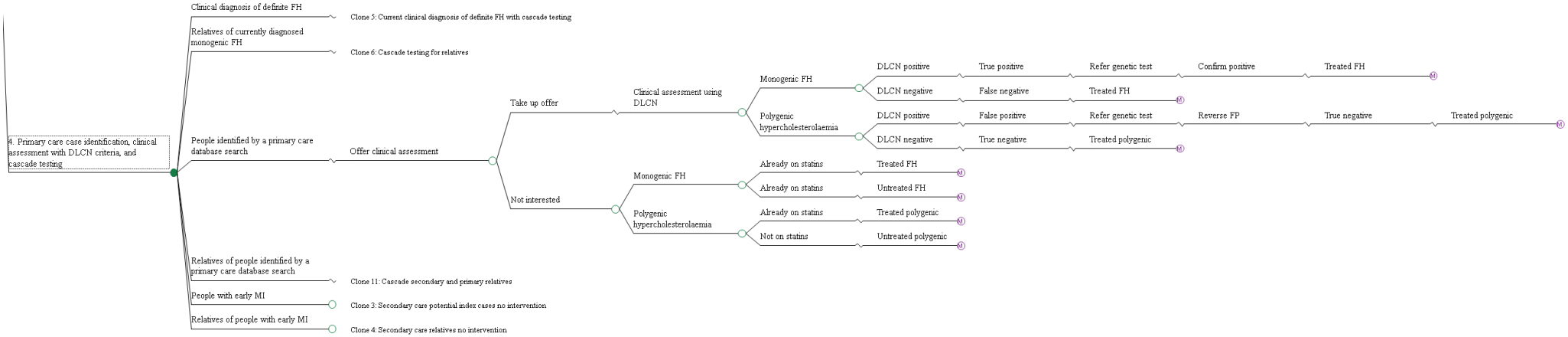
The following diagrams show the structure of the short term identification and diagnosis module. The structure of the long term modules has been described in NICE Clinical Guideline 181 with adaptions reported in the main article.

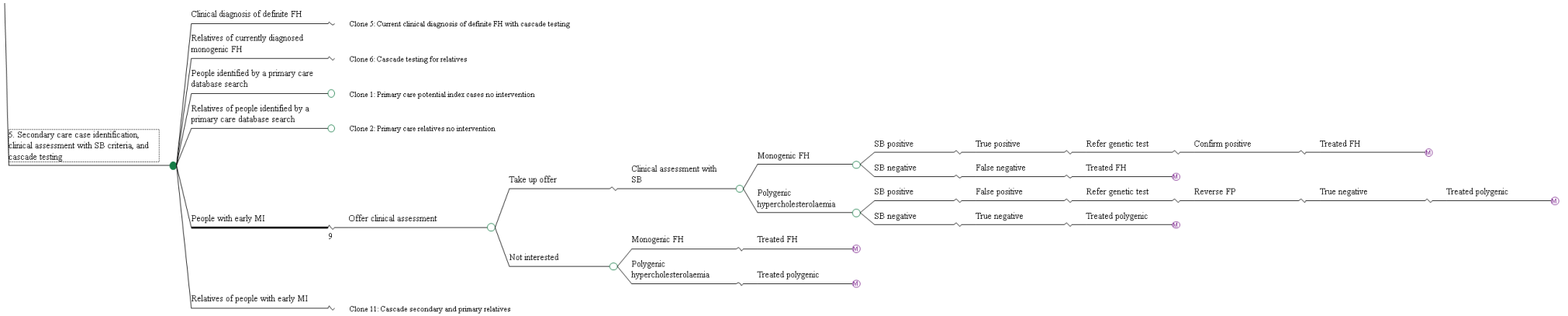


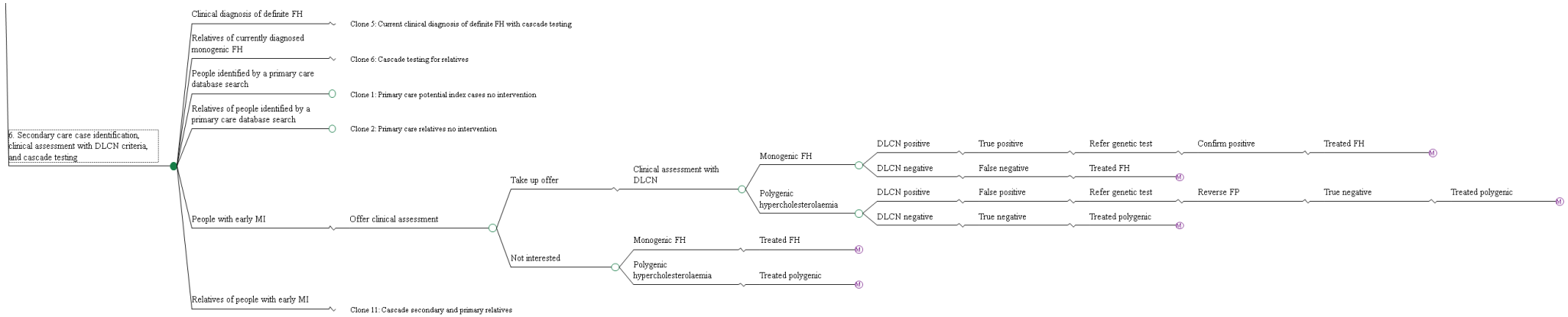

1. No cascade testing or case identification
Clinical diagnosis of definite FH
Monogenic FH
Treated FH
Polygenic hypercholesterolaemia
Treated polygenic
Relatives of currently diagnosed monogenic FH
Monogenic FH
Untreated FH
No FH
Healthy
People identified by a primary care database search
Monogenic FH
Already on statins
Treated FH
Not already on statins
Untreated FH
Polygenic hypercholesterolaemia
Already on statins
Treated polygenic
Not already on statins
Untreated polygenic
Relatives of people identified by a primary care database search
Monogenic FH
Untreated FH
No FH
Healthy
People with early MI
Monogenic FH
Treated FH
Polygenic hypercholesterolaemia
Treated polygenic
Relatives of people with early MI
Monogenic FH
Untreated FH
No FH
Healthy

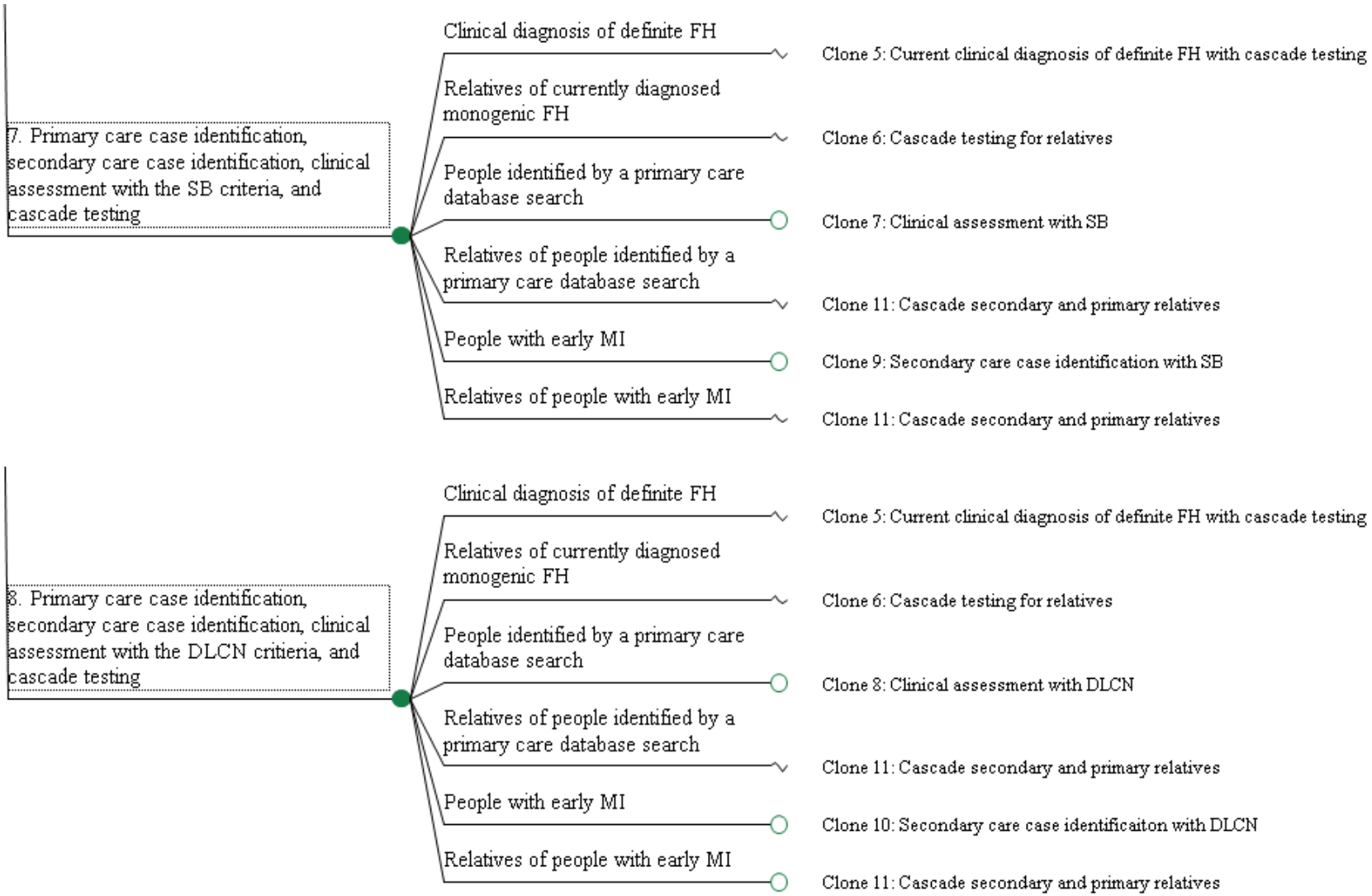

2. Cascade testing
Clinical diagnosis of definite FH
Agree to genetic test prior to cascade relatives
Genetic test
Monogenic FH
Treated FH
Polygenic Hypercholesterolaemia
Treated polygenic
Don't agree to genetic test prior to cascade relatives
Monogenic FH
Treated FH
Polygenic Hypercholesterolaemia
Treated polygenic
Relatives of currently diagnosed monogenic FH
Index case agreed to genetic testing
Contact and offer genetic testing
Take up offer
Monogenic FH
Treated FH
No FH
Healthy
Not interested
Monogenic FH
Untreated FH
No FH
Healthy
Index case did not agree to genetic testing
Monogenic FH
Untreated FH
No FH
Healthy
People identified by a primary care database search
Clone 1: Primary care potential index cases no intervention
Relatives of people identified by a primary care database search
Clone 2: Primary care relatives no intervention
People with early MI
Clone 3: Secondary care potential index cases no intervention
Relatives of people with early MI
Clone 4: Secondary care relatives no intervention

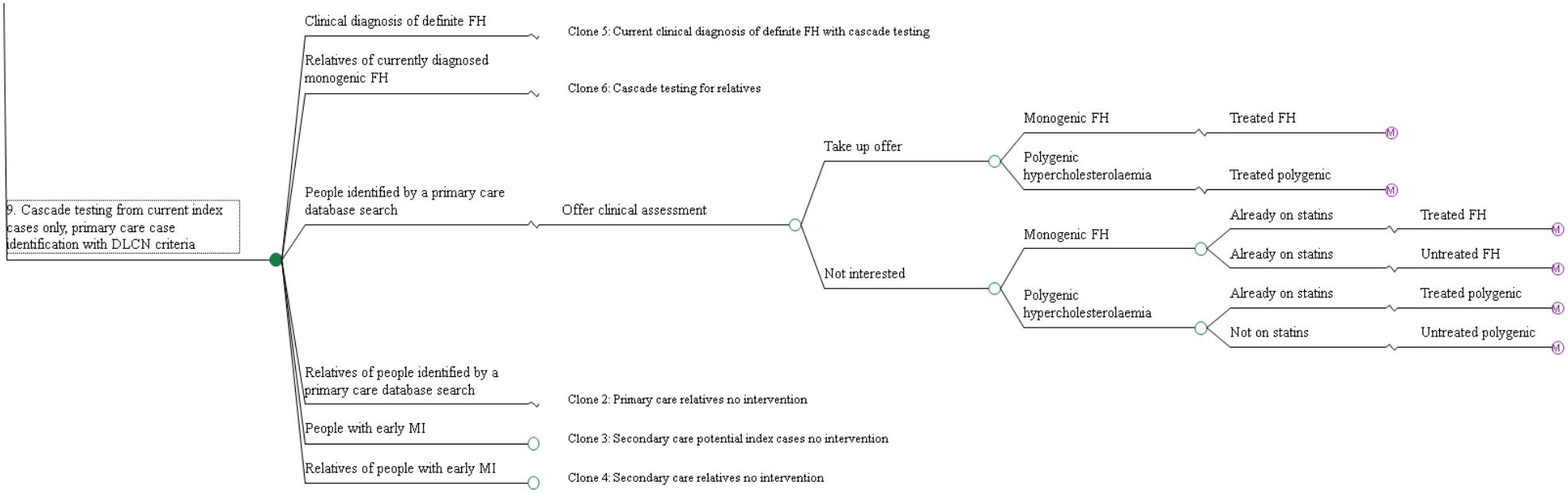

3. Primary care case identification, clinical assessment with SB criteria, and cascade testing
Clinical diagnosis of definite FH
Clone 5: Current clinical diagnosis of definite FH with cascade testing
Relatives of currently diagnosed monogenic FH
Clone 6: Cascade testing for relatives
People identified by a primary care database search
Offer clinical assessment
Take up offer
Clinical assessment using SB
Monogenic FH
SB positive
True positive
Refer genetic test
Confirm positive
Treated FH
SB negative
False negative
Treated FH
Polygenic hypercholesterolaemia
SB positive
False positive
Refer genetic test
Reverse FP
True negative
Treated polygenic
SB negative
True negative
Treated polygenic
Not interested
Monogenic FH
Already on statins
Treated FH
Not on statins
Untreated FH
Polygenic hypercholesterolaemia
Already on statins
Treated polygenic
Not on statins
Untreated polygenic
Relatives of people identified by a primary care database search
New index case takes up offer and correctly diagnosed
Contact and offer genetic testing
Take up offer
Monogenic FH
Treated FH
No FH
Healthy
Not interested
Monogenic FH
Untreated FH
No FH
Healthy
New index case not interested or incorrectly diagnosed
Monogenic FH
Untreated FH
No FH
Healthy
People with early MI
Clone 3: Secondary care potential index cases no intervention
Relatives of people with early MI
Clone 4: Secondary care relatives no intervention


4. Primary care case identification, clinical assessment with DLCN criteria, and cascade testing
Clinical diagnosis of definite FH
Clone 5: Current clinical diagnosis of definite FH with cascade testing
Relatives of currently diagnosed monogenic FH
Clone 6: Cascade testing for relatives
People identified by a primary care database search
Offer clinical assessment
Take up offer
Clinical assessment using DLCN
Monogenic FH
DLCN positive
True positive
Refer genetic test
Confirm positive
Treated FH
DLCN negative
False negative
Treated FH
Polygenic hypercholesterolaemia
DLCN positive
False positive
Refer genetic test
Reverse FP
True negative
Treated polygenic
DLCN negative
True negative
Treated polygenic
Not interested
Monogenic FH
Already on statins
Treated FH
Already on statins
Untreated FH
Polygenic hypercholesterolaemia
Already on statins
Treated polygenic
Not on statins
Untreated polygenic
Relatives of people identified by a primary care database search
Clone 11: Cascade secondary and primary relatives
People with early MI
Clone 3: Secondary care potential index cases no intervention
Relatives of people with early MI
Clone 4: Secondary care relatives no intervention


5. Secondary care case identification, clinical assessment with SB criteria, and cascade testing
Clinical diagnosis of definite FH
Clone 5: Current clinical diagnosis of definite FH with cascade testing
Relatives of currently diagnosed monogenic FH
Clone 6: Cascade testing for relatives
People identified by a primary care database search
Clone 1: Primary care potential index cases no intervention
Relatives of people identified by a primary care database search
Clone 2: Primary care relatives no intervention
People with early MI
9
Offer clinical assessment
Take up offer
Clinical assessment with SB
Monogenic FH
SB positive
True positive
Refer genetic test
Confirm positive
Treated FH
SB negative
False negative
Treated FH
Polygenic hypercholesterolaemia
SB positive
False positive
Refer genetic test
Reverse FP
True negative
Treated polygenic
SB negative
True negative
Treated polygenic
Not interested
Monogenic FH
Treated FH
Polygenic hypercholesterolaemia
Treated polygenic
Relatives of people with early MI
Clone 11: Cascade secondary and primary relatives


6. Secondary care case identification, clinical assessment with DLCN criteria, and cascade testing
Clinical diagnosis of definite FH
Clone 5: Current clinical diagnosis of definite FH with cascade testing
Relatives of currently diagnosed monogenic FH
Clone 6: Cascade testing for relatives
People identified by a primary care database search
Clone 1: Primary care potential index cases no intervention
Relatives of people identified by a primary care database search
Clone 2: Primary care relatives no intervention
People with early MI
Offer clinical assessment
Take up offer
Clinical assessment with DLCN
Monogenic FH
DLCN positive
True positive
Refer genetic test
Confirm positive
Treated FH
DLCN negative
False negative
Treated FH
Polygenic hypercholesterolaemia
DLCN positive
False positive
Refer genetic test
Reverse FP
True negative
Treated polygenic
DLCN negative
True negative
Treated polygenic
Not interested
Monogenic FH
Treated FH
Polygenic hypercholesterolaemia
Treated polygenic
Relatives of people with early MI
Clone 11: Cascade secondary and primary relatives


7. Primary care case identification, secondary care case identification, clinical assessment with the SB criteria, and cascade testing
Clinical diagnosis of definite FH
Clone 5: Current clinical diagnosis of definite FH with cascade testing
Relatives of currently diagnosed monogenic FH
Clone 6: Cascade testing for relatives
People identified by a primary care database search
Clone 7: Clinical assessment with SB
Relatives of people identified by a primary care database search
Clone 11: Cascade secondary and primary relatives
People with early MI
Clone 9: Secondary care case identification with SB
Relatives of people with early MI
Clone 11: Cascade secondary and primary relatives
8. Primary care case identification, secondary care case identification, clinical assessment with the DLCN critieria, and cascade testing
Clinical diagnosis of definite FH
Clone 5: Current clinical diagnosis of definite FH with cascade testing
Relatives of currently diagnosed monogenic FH
Clone 6: Cascade testing for relatives
People identified by a primary care database search
Clone 8: Clinical assessment with DLCN
Relatives of people identified by a primary care database search
Clone 11: Cascade secondary and primary relatives
People with early MI
Clone 10: Secondary care case identificaiton with DLCN
Relatives of people with early MI
Clone 11: Cascade secondary and primary relatives

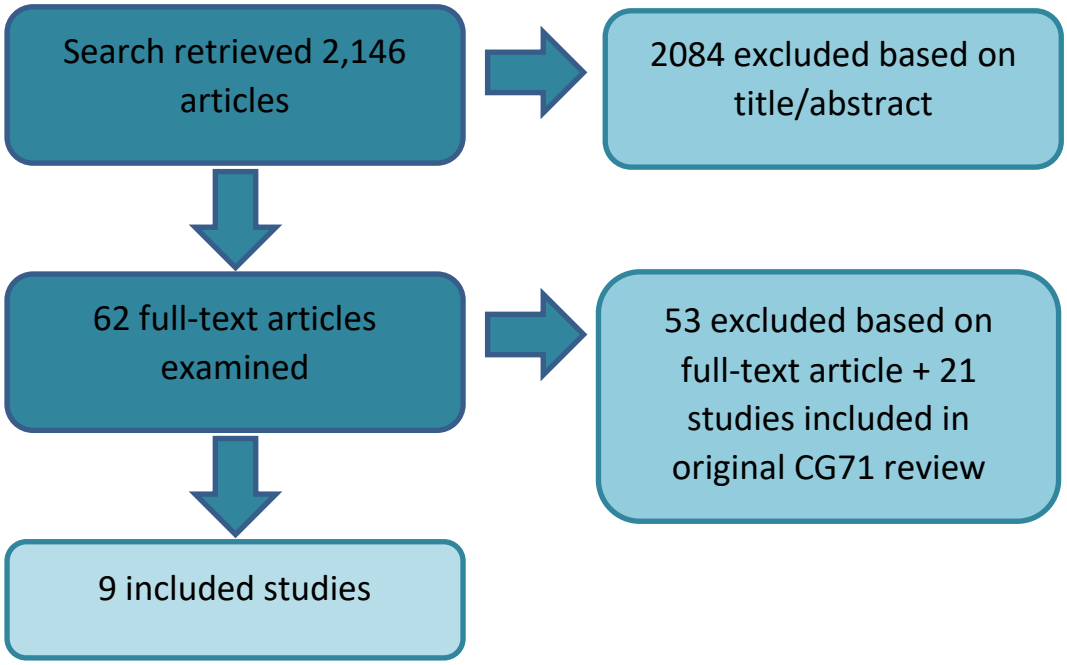

9. Cascade testing from current index cases only, primary care case identification with DLCN criteria
Clinical diagnosis of definite FH
Clone 5: Current clinical diagnosis of definite FH with cascade testing
Relatives of currently diagnosed monogenic FH
Clone 6: Cascade testing for relatives
People identified by a primary care database search
Offer clinical assessment
Take up offer
Monogenic FH
Treated FH
Polygenic hypercholesterolaemia
Treated polygenic
Not interested
Monogenic FH
Already on statins
Treated FH
Already on statins
Untreated FH
Polygenic hypercholesterolaemia
Already on statins
Treated polygenic
Not on statins
Untreated polygenic
Relatives of people identified by a primary care database search
Clone 2: Primary care relatives no intervention
People with early MI
Clone 3: Secondary care potential index cases no intervention
Relatives of people with early MI
Clone 4: Secondary care relatives no intervention

3 Assumptions

- Genetic testing has perfect sensitivity and specificity. The committee discussed the potential impact of variants of unknown clinical significance (VUCS) and decided not to include this in the model because VUS occur in only ~5% of genetic tests and not at all in testing relatives of mutation positive cases. In addition, the approach to management would be similar to someone with confirmed FH apart from cascade testing their relatives. Consequently, false positives are not possible by the end of the diagnostic pathway. A false positive *clinical* diagnosis is possible but this is correct by subsequent genetic testing and converted to a true positive. This assumption was not the subject of sensitivity analysis but is explored in the discussion section. A false negative clinical diagnosis is possible and this is not corrected by subsequent genetic testing because this cohort would not be referred for it.
- All people with early MI (potential new index cases in secondary care) receive treatment with high-intensity statins regardless of whether their FH status is known or not. Therefore, any benefit (and long term cost) of strategies that involve case identification in secondary care stems from cascade testing the relatives of new index cases.
- A proportion of people with previously undiagnosed FH identified by a primary care database search who do not come into contact with a health care provider are assumed to be already appropriately treated with high intensity statins or ezetimibe due to having a high prior cholesterol reading. This proportion is assumed to be the same as the polygenic population, 19.3% in the base case based on an evaluation of the NHS Health Check.[1]
- If people with FH identified by a primary care database search take up clinical assessment, they receive appropriate treatment regardless of whether the clinical assessment diagnoses them with FH or not due to blood tests that show they have high cholesterol and influence of the additional contact with primary care. The impact of this assumption is that false negatives that result from clinical assessment are assigned to the 'Treated FH' long term module even though they do not have a genetic test. This is considered a conservative approach to this issue.
- A single probability of take up was used for each subgroup representing the acceptance of clinical assessment, referral to a lipid clinic, and genetic testing. In reality, there is the potential for people to take up clinical assessment but not proceed to consultation at the lipid clinic or genetic testing following that. However, insufficient data was available to inform additional take up probabilities based on the systematic review conducted for the case finding review question. The probability of take up adopted for each subgroup was taken from published literature and agreed with the committee.
- There is 100% adherence to the treatment once disease is diagnosed. This is consistent with the approach of the lipid modification model in NICE CG181. The focus of the present model is case identification and diagnosis and topic experts advised that, in their experience, adherence is quite high in the population with FH. In practice, the committee advised that while people are likely to pick up their prescriptions (and thus incur costs), a proportion would not adhere to treatment. This limitation was judged as minor as efficacy estimates for statins were drawn from trials that contained a proportion of non-adherents but allocated according to intention to treat.
- All relatives are assumed to not know their FH status, cholesterol level or be currently treated with statins. This is a strong assumption but was assessed as minor in the context of the conservatively small number of relatives assumed to be identified per index case.

- Relatives either have FH or they do not and are ‘healthy’. That is, a simplifying assumption was made that relatives who have the potential to be cascade tested because a direct relative has genetically confirmed FH do not have polygenic hypercholesterolaemia.
- Crossover between interventions has not been accounted for in the model. In practice, a primary care database search may identify relatives of current index cases who have already been cascade tested and vice versa. However, no data was identified in the published literature to inform an alternative approach.

4 Systematic review flowchart for diagnostic accuracy of clinical assessment tools



5 Additional detail on input parameters

5.1 People with a current clinical diagnosis of FH

The number of people with a current clinical diagnosis of FH was informed by an audit of lipid clinics in the UK in 2010.[2] The proportion of people with a current clinical diagnosis that actually had a functional mutation in the *LDLR*, *APOB* or *PSK9PSK9* gene was taken from the experience of the Welsh, Scottish and Wessex FH services.[3] A conservative estimate of 1/500 was used for the prevalence of FH in the general population.[4] This was varied up to 1/217 in sensitivity analysis.[5]

5.2 People identified by a primary care database search

The size of the adult population of England and Wales was used to represent the number of people registered in primary care databases and sourced from the Office of National Statistics.

The availability of relevant cholesterol data was estimated at 31% in the UK context.[6,7] This value affects the overall resource impact but not the cost-effectiveness of primary care case finding as there are few fixed costs within the model. The take up of clinical assessment by people identified by a primary care database search was informed by the general practice and workplace identification cohorts of an Australian study.[8]

5.3 People with early myocardial infarction

The prevalence of FH in people with early myocardial infarction (MI) was informed by a UK study of people genetically tested for *LDLR* gene deletions or duplications.[9] In sensitivity analysis, this was varied between the lower 95% confidence interval from the same study up to an alternative mean estimate from a study based on clinical assessment to diagnose FH in the secondary care setting.[9,10] The take up of clinical assessment and genetic testing by people with early MI was informed by the UK study of genetically-confirmed prevalence and varied arbitrarily 25% higher and lower than this estimate in sensitivity analysis.[9] The prevalence of people with early MI was sourced from a summary of the epidemiology of cardiovascular disease in the UK.[11]

5.4 Relatives

The number of relatives invited for cascade testing per index case was estimated from a finding that 1.33 relatives were genetically tested per index case in the Scottish, Welsh and Wessex FH services and that 59.89% relatives take up cascade testing (1.33/0.5989 = 2.22).[3,12] Therefore, this parameter was varied in sensitivity analysis between 1 relative, based on a worst-case scenario, and 12 relatives, based on an optimistic assumption used in a previous NICE costing report from 2009.

Take up by relatives of cascade testing from people with a current clinical diagnosis and take up by relatives of clinical assessment and genetic testing from people identified by a primary care database search, 59.89%, was sourced from a UK audit of FH services and varied arbitrarily 25% higher and lower in sensitivity analysis.[12] The same parameters were assumed for the take up by relatives of people identified by a secondary care database search in the absence of data directly applicable to that population.

Table 1: Key input parameters, case identification and cascade testing

Parameter	Amount	Source
People with a current clinical diagnosis of FH (current index cases)		
Number of people with a current clinical diagnosis of possible or definite FH	18,000	RCP 2010 (UK FH audit), 15% of 120k (number under active management in UK lipid clinics)[2]
Proportion of current clinical diagnosis with definite FH with monogenic mutation	22.98%	Welsh, Scottish & Wessex FH services, cited in Kerr et al. 2017[3]
Prevalence monogenic FH in general population	0.20%	Nordestgaard 2013, 1 in 500, conservative lower limit found in literature[4]
Take up of genetic testing by people with a current clinical diagnosis of FH prior to cascade testing	84.10%	Median from clinical review[13]
People identified by primary care database search (potential new index cases)		
Population of England and Wales	45,579,669	Office of National Statistics 2015 (age 18+)
Proportion database search that warrant further investigation	0.51%	Futema 2015 TC >9.3 (base case)[6]
Number of people identified by primary care database search	54,069	Calculated: population of England & Wales * proportion warranting further investigation * take up rate -currently diagnosed FH
Prevalence of FH in people identified by primary care database search	28.00%	Futema 2015 TC >9.3 (base case)[6]
Proportion of people with high cholesterol already on statins	19.30%	Robson 2016, NHS Health Check[1]
Take up of clinical assessment and genetic testing by people identified by primary care database search	26.03%	Kirke et al. 2015, general practice database and work place assessment[8]
Proportion of people with necessary data in database	30.97%	Calculated: 831/(7.3% x (6127x6))[6,7]
People with early myocardial infarction (potential new index cases in secondary care)		
Number of people with early MI (secondary care)	104,833	Calculated: population of England & Wales x prevalence of MI
Prevalence of FH in people with early MI (secondary care)	1.30%	Wald et al. 2015[9]
Take up of clinical assessment and genetic testing by people with early MI	72.50%	Wald et al. 2015 (% excluding declined and too unwell)[9]
Prevalence of MI in general population	0.23%	Prevalence MI age<55 from Bhatnagar 2015, adjusted for age and sex from ONS 2015[11]

Relatives		
Number of relatives of index cases with FH	8,438	Calculated: no. with current FH * relatives per index case * probability of FH among relatives
Number of relatives of people with FH identified through primary care database search	32,259	Calculated: number at risk in primary care * prevalence of FH in that population * no of relatives per index case
Number of relatives of people with FH that have had an early MI (secondary care)	2,780	Calculated: number at risk in secondary care * prevalence of FH in that population * no of relatives per index case
Number of relatives invited for cascade testing per index case	2.22	Calculated: 1.33 genetically tested (Kerr et al 2017) / 59.89% proportion take up that were invited (Hadfield 2009). This is the number of relatives per (index case with genetically confirmed FH) that are invited for cascade testing regardless of whether they take up the offer or actually have FH.[3,12]
Probability tested relative has monogenic FH	50.89%	Welsh, Scottish & Wessex FH services, cited in Kerr et al. 2017 [3]
Take up by relatives of cascade testing from currently diagnosed FH population	59.89%	Clinical review: Hadfield 2009[12]
Take up by relatives of clinical assessment and genetic testing from people identified in primary care	59.89%	Clinical review: Hadfield 2009[12]
Take up by relatives of clinical assessment and genetic testing from people with early MI (secondary care)	59.89%	Assume same as primary care relatives

5.5 Long term health outcomes for treated and untreated familial hypercholesterolaemia

People with FH are at an increased risk of experiencing four of the CVD events in the economic model for CG181: stable angina, unstable angina, myocardial infarction and death due to CHD. The increased risk of coronary heart disease due to FH was based on data from the Simon Broome Register Group which reported on the mortality of a UK cohort over multiple decades with standardised mortality ratios reported by age and sex (personal communication, S. Humphries).[14] The increased risk of mortality was extrapolated to represent non-fatal events in the absence of similarly granular data from alternative sources. Extrapolating mortality data to represent non-fatal cardiac events was consistent with prior economic analyses on FH.[3,15-17] Relative risks calculated only in patients before the statin era were preferable as they would be more representative of the true risks associated with FH but were only used in sensitivity analysis due to lack of statistical power.

The risks of the following events were left the same as the general population: transient ischaemic attack, stroke, heart failure and peripheral artery disease. Two alternative sources were considered but did not report data in a format relevant to the model.[5,18] Benn et al. provided a summary adjusted odds ratio of 3.3 (95% CI 1.7 to 6.4) for *LDLR* carriers and 1.3 (95% CI 0.6 to 2.5) for *APOB* carriers as well as odds ratios specifically for MI.[5] However, this study was based on a Danish cohort and odds ratios are not reported separately by age and sex. Khera et al. provide a summary odds ratio for CAD of 3.8 (95% CI 2.6 to 5.4).[18] However, this study was based on an American cohort and

odds ratios are not reported by age or sex. The increased risk of CVD due to FH was tested in sensitivity analysis by arbitrarily doubling and halving the relative risk relative to 1.

The *relative* treatment effect of lipid modification on CVD risk was assumed to be the same in the FH population as in the general population due to a lack of evidence on the adult FH population identified in the systematic review conducted for the update to the NICE guideline. Placebo-controlled trials have not included people with FH because it is unethical to withhold treatment from patients with severe hypercholesterolaemia due to high lifetime risk of CHD. Appropriate treatment with statins was assumed to result in the same *relative* reduction in CVD event risk whether that was achieved with statins or ezetimibe or a combination of both in the base case.

Although the relative treatment effect was the same as that used in the CG181 economic model, the *absolute* risk of CHD for treated FH was still raised compared with the general population. Two studies supported this continued increased *absolute* risk associated with FH despite treatment.[19,20] Two studies found this risk to be reduced to the same level as the general population.[21,22] However, the cohorts compared by Versmissen et al. were older with a mean age of 61.6 years and contained only 24.5% men. Considering all 4 studies were based on a clinical diagnosis (rather than genetic) and, therefore, contained a potentially large polygenic cohort, a conservative approach was taken and higher absolute risk of CHD retained with treatment in the base case. The treatment effects were heightened to the limit of their observed confidence intervals in all clinical domains in sensitivity analysis to move treated risk closer to that of the overall population. A recent study of a Spanish cohort suggested that the base case risks of CHD events may have been too high.[23] A sensitivity analysis was conducted in which the model outputs for patients with treated FH were calibrated to match the outcomes observed in this trial.

5.6 Diagnostic accuracy of clinical assessment tools

The accuracy of the SB and DLCN diagnostic criteria was established through systematic review and meta-analysis with summary figures provided in Table 2. A systematic search was conducted which identified 2,146 articles. The titles and abstracts were screened and 62 articles were identified as potentially relevant. Full-text versions of these articles were ordered and reviewed against criteria established in an earlier review protocol prepared in collaboration with topic experts. Of these, 53 were excluded as they did not meet the criteria and nine studies were included. One of the key requirements for inclusion was that the diagnostic accuracy of the clinical assessment tool had to be established by comparison with a genetic test for mutations in the *LDLR, APOB* or *PCSK9* genes. Six studies addressed the effectiveness of the DLCN criteria.[8,24-28] Four studies addressed both the DLCN and SB criteria.[26,29-31]

Meta-analysis was conducted where four or more studies were available based on a bivariate model using the *mada* package in R v3.3.1. This package accounts for the correlations between sensitivity and specificity. Where sufficient data were not available, separate pooling was performed for sensitivity and specificity using Microsoft Excel, treating the data as simple proportions. This approach is likely to somewhat underestimate test accuracy as it fails to account for the correlation and trade-off between sensitivity and specificity. Random-effects models were fitted for all syntheses. Diagnostic accuracy was calculated at different thresholds of the assessment tools. For example, possible or definite FH under the SB criteria and definite only under the SB criteria.

In the base case a more inclusive 'rule out' profile was used for referral to a lipid clinic and genetic testing: possible or definite according to the SB criteria and a score >5 for the DLCN criteria because sensitivity was prioritised over specificity by the NICE guideline committee. Sensitivity analysis using the 'definite' only criteria for each tool was also examined.

Table 2: Sensitivity and specificity of clinical assessment tools

Clinical assessment tool and threshold	Sensitivity	Specificity
Possible/probable and definite FH		
SB possible or definite FH	0.890	0.287
DLCN probable or definite FH (score >5)	0.861	0.457
Definite FH only		
SB definite FH	0.360	0.940
DLCN definite FH (score >8)	0.567	0.802

5.7 Long term outcomes for treated and untreated polygenic hypercholesterolaemia

Economic modelling conducted for NICE's clinical guideline on lipid modification was used to derive the risk of cardiac events, reduction in this risk due to treatment and how this translates into improved survival and quality of life as accumulated through QALYs.[32] The CG181 model allows the user to specify underlying risk scores based on the QRISK algorithm and the age and sex of patients who are then tracked over time and experience cardiovascular events (including myocardial infarction, stroke, transitory ischaemic attack, heart failure, peripheral arterial disease, stable and unstable angina) that affect their quality of life and mortality.[33] The probabilities of these events occurring are reduced by the use of statins (Table 3). No changes were made to the clinical aspects of this model for the cohorts with polygenic hypercholesterolaemia. Treatment was based on atorvastatin 20mg, as recommended in CG181. A full description of the model can be found in the appendixes of CG181.[32]

Table 3: Treatment effect on CVD risk

CVD event	Relative risk (base case)	Relative risk (low sensitivity analysis)	Relative risk (high sensitivity analysis)
Stable angina	0.46	0.37	0.59
Unstable angina	0.46	0.37	0.59
Myocardial infarction	0.46	0.37	0.59
Transient ischaemic attack	0.8	0.7	0.91
Stroke	0.8	0.7	0.91
Heart failure	1	1	1
Peripheral artery disease	0.46	0.37	0.59
Cardiovascular mortality	0.73	0.61	0.88
Non-cardiac mortality	0.96	0.87	1.16

5.8 Long term health outcomes for treated and untreated familial hypercholesterolaemia

People with FH are at an increased risk of experiencing four of the CVD events in the economic model for CG181: stable angina, unstable angina, myocardial infarction and death due to CHD. The increased risk of coronary heart disease due to FH was based on data from the Simon Broome Register Group which reported on the mortality of a UK cohort over multiple decades with standardised mortality ratios reported by age and sex (personal communication, S. Humphries).[14] The increased risk of mortality was extrapolated to represent non-fatal events in the absence of similarly granular data from alternative sources. Extrapolating mortality data to represent non-fatal cardiac events was consistent with prior economic analyses on FH.[3,15-17] Relative risks calculated only in patients before the statin era were preferable as they would be more representative of the true risks associated with FH but were only used in sensitivity analysis due to lack of statistical power.

The risks of the following events were left the same as the general population: transient ischaemic attack, stroke, heart failure and peripheral artery disease. Two alternative sources were considered but did not report data in a format relevant to the model.[5,18] Benn et al. provided a summary adjusted odds ratio of 3.3 (95% CI 1.7 to 6.4) for *LDLR* carriers and 1.3 (95% CI 0.6 to 2.5) for *APOB* carriers as well as odds ratios specifically for MI.[5] However, this study was based on a Danish cohort and odds ratios are not reported separately by age and sex. Khera et al. provide a summary odds ratio for CAD of 3.8 (95% CI 2.6 to 5.4).[18] However, this study was based on an American cohort and odds ratios are not reported by age or sex. The increased risk of CVD due to FH was tested in sensitivity analysis by arbitrarily doubling and halving the relative risk relative to 1.

The relative treatment effect of lipid modification on CVD risk was assumed to be the same in the FH population as in the polygenic population due to a lack of evidence on the adult FH population identified in the systematic review conducted for the update to the NICE guideline. Placebo-controlled trials have not included people with FH because it is unethical to withhold treatment from patients with severe hypercholesterolaemia due to high lifetime risk of CHD. Appropriate treatment with statins was assumed to result in the same relative reduction in CVD event risk whether that was achieved with statins or ezetimibe or a combination of both in the base case.

Although the relative treatment effect was the same as that used in the CG181 economic model, the absolute risk of CHD for treated FH was still raised compared with the general and polygenic populations. Two studies supported this continued increased absolute risk associated with FH despite treatment.[19,20] Two studies found this risk to be reduced to the same level as the general population.[21,22] However, the cohorts compared by Versmissen et al. were older with a mean age of 61.6 years and contained only 24.5% men. Considering all 4 studies were based on a clinical diagnosis (rather than genetic) and, therefore, contained a potentially large polygenic cohort, a conservative approach was taken and higher absolute risk of CHD retained with treatment in the base case. The treatment effects were heightened to the limit of their observed confidence intervals in all clinical domains in sensitivity analysis to move treated risk closer to that of the overall population. One limitation of this overall modelling approach was that it calculated costs and QALYs incorrectly for the very small subpopulation of this model who have already had an early MI. This limitation was minor, however, as this population was exactly the same among strategies so any error would have cancelled out and the relative cost effectiveness results were unaffected.

Table 4: Relative risk of coronary heart disease due to FH in males, females and combined

Age	Males (first events)	Females (first events)	Combined (combined)
40	4.0028	5.133	4.179
45	4.0028	5.133	4.179
55	4.0028	5.133	4.179
65	1.6199	2.2827	1.8842
75	1.6199	2.2827	1.8842
85	1.6199	2.2827	1.8842

6 Long term results

After adjusting for age, the Markov modules resulted in the mean payoffs for the four cohorts specified in Table 5. These figures represented the expected total, discounted cost and health outcomes experienced by each cohort over their lifetimes. Differences in QALYs and costs between males and females were predominantly due to different baseline risks of cardiovascular events and different adjustments in those risks due to FH. People with FH gain more costs and less QALYs from their significantly higher risk of experiencing cardiovascular events. These costs were weighted by age group within each sex and by possible baseline QRISK score of the polygenic population. In the absence of data on the prevalence of different QRISK scores among the population of interest, equal weight was given to QRISKs for 10%, 15%, 20%, 25% and 30%. This was varied from 100% of people have a QRISK of 10% to 100% of people having a QRISK of 30% in sensitivity analysis. The figures in Table 5 show that if a case of FH can be found, it is highly cost effective to treat. Indeed, it may be cost saving especially for women and men of younger ages due to the large reduction in CVD event costs outweighing the cost of high intensity statins.

Table 5: Expected lifetime costs and QALYs

Payoff	Treated FH	Untreated FH	Treated polygenic	Untreated polygenic
Male - cost	£12,045.05	£12,347.77	£6,270.82	£6,286.97
Male - QALYs	12.13	11.22	12.97	12.35
Females - cost	£12,737.57	£13,237.78	£5,994.42	£5,765.35
Females - QALYs	12.39	11.47	13.32	12.68

7 Values used in univariate sensitivity analysis

Parameter	Low value	High value	Source
Prevalence monogenic FH in general population	0.20%	0.46%	Upper: Benn et al. 2016; lower same as base case
Take up of genetic testing by people with a current clinical diagnosis of FH prior to cascade testing	69.10%	98.9%	Range from clinical review
Proportion database search that warrant further investigation	0.50%	2.36%	Futema 2015, total cholesterol >9.3mmol/L
Prevalence of FH in people identified by primary care database search	15%	41.18%	Futema 2015 range
Proportion of people with high cholesterol already on statins	10%	99.00%	Expert advice
Take up of clinical assessment and genetic testing by people identified by primary care database search	26%	50%	Expert advice
Prevalence of FH in people with early MI (secondary care)	0.30%	8.30%	Lower: 95% CI Wald 2015; Higher: De Backer 2015
Take up of clinical assessment and genetic testing by people with early MI	54.38%	90.63%	25% higher and lower than expected
Number of relatives invited for cascade testing per index case	2	12	NICE CG71 Costing Report 2009
Take up by relatives of cascade testing from currently diagnosed FH population	44.92%	74.86%	25% higher and lower than expected
Take up by relatives of clinical assessment and genetic testing from people identified in primary care	44.92%	74.86%	25% higher and lower than expected
Take up by relatives of clinical assessment and genetic testing from people with early MI (secondary care)	44.92%	74.86%	25% higher and lower than expected
Cost of genetic testing index case	£287.00	£460.00	UK genetic testing network
Cost of genetic testing relative	£75.00	£175.00	UK genetic testing network

8 Probabilistic sensitivity analysis distributions and parameter settings

Parameter	Distribution	alpha	beta
Proportion database search that warrant further investigation	beta	831	34,607
Prevalence of FH in people identified by primary care database search	beta	24	1,362
Take up of clinical assessment and genetic testing by people identified by primary care database search	beta	719	2,042
Prevalence of FH in people with early MI (secondary care)	beta	2	158
Take up of clinical assessment and genetic testing by people with early MI	beta	167	63
Take up by relatives of cascade testing from currently diagnosed FH population	beta	768	515
Take up by relatives of clinical assessment and genetic testing from people identified in primary care	beta	768	515
Take up by relatives of clinical assessment and genetic testing from people with early MI (secondary care)	beta	768	515
Sensitivity Simon Broome possible or definite FH	correlated to spec		
Specificity Simon Broome possible or definite FH	beta	8.21	20.38
Sensitivity Simon Broome definite FH	correlated to spec		
Specificity Simon Broome definite FH	beta	9.99	0.64
Sensitivity DLCN probable, definite FH (>=6)	correlated to spec		
Specificity DLCN probable, definite FH (>=6)	beta	21.61	25.68
Sensitivity DLCN definite FH (>8)	correlated to spec		
Specificity DLCN definite FH (>8)	beta	79.61	19.66

9 Short term costs

The following tables present the derivation of costs used to inform the short term case identification and diagnosis module. The totals, or 'expected cost' for each subgroup are the total costs adjusted for the probability of the individual costs occurring.

Most of the costs are listed for each individual resource (such as a genetic test or 15 minutes of specialist nurse time) with the exception of staff input that occurs directly before and after a genetic test. These estimates were sourced from Kerr et al.[3] and are based on the resource use in the Welsh, Scottish and Wessex FH services with the latest costs from the PSSRU[34] applied. There are four options for this cost that could be incurred depending on the subgroup and whether the genetic test is positive or negative. For index cases, the costs are higher due to the additional time and resource required for genetic counselling but less when the test is negative and treatment options and cascade testing do not need to be discussed. Genetic testing for relatives costs less than index cases because the family mutation is known, so it is a less time consuming process.

Table 6: Cost of genetic testing, index cases

Laboratory	NHS Price	Source
Bristol RGC	£287.00	Bristol, personal communication 07.02.2017
London North East RGC GOSH	£460.00	https://ukgtn.nhs.uk/, 07.02.2017
Liverpool RGC	£375.00	https://ukgtn.nhs.uk/, 07.02.2017
Cardiff RGC	£350.00	https://ukgtn.nhs.uk/, 07.02.2017
Sheffield RGC	£400.00	https://ukgtn.nhs.uk/, 07.02.2017

Table 7: Cost of genetic testing, relatives

Laboratory	NHS Price	Source
London North East RGC GOSH	£130.00	https://ukgtn.nhs.uk/, 07.02.2017
Liverpool RGC	£75.00	https://ukgtn.nhs.uk/, 07.02.2017
Sheffield RGC	£105.00	https://ukgtn.nhs.uk/, 07.02.2017
Cardiff RGC	£160.00	https://ukgtn.nhs.uk/, 07.02.2017
Salisbury RGC	£175.00	https://ukgtn.nhs.uk/, 07.02.2017
Bristol RGC	£77.00	https://ukgtn.nhs.uk/, 07.02.2017

Table 8: Healthcare admin and staff support for genetic testing

Action	Resource	Amount
Polygenic index cases		
Consultation to plan genetic testing	20 minutes medical consultant	£60.74
Arrangement of DNA test	10 minutes admin assistant	£4.00
Take blood sample and send to DNA service	1 hour specialist nurse band 7	£131.00
Notification of test results	10 minutes admin assistant	£4.00
Total polygenic index cases		£199.74

Additional costs for mutation-positive index cases		
Follow-up consultation with test result	30 minutes specialist nurse	£65.50
Draw family tree and discuss cascade testing	1 hour genetic counsellor	£131.00
Total mutation-positive FH index cases		£396.24
Mutation-negative relatives		
Take blood sample and send to DNA service	1 hour specialist nurse	£131.00
Provide test result	20 minutes genetic counsellor	£43.67
Total mutation-negative relatives		£174.67
Additional costs for mutation-positive relatives		
Follow-up consultation, prescribe statins	40 minutes consultant or specialist nurse	£104.40
Total mutation-positive relatives		£279.07

Table 9: Unit costs for short term case identification and diagnosis module

Model Input	Cost	Source
Genetic test, index case, family mutation unknown (each)	£375.00	UK Genetic Testing Network website (median value used)
Genetic test, relative of index case, family mutation known (each)	£117.50	UK Genetic Testing Network website (median value used)
Primary care nurse specialist	£75.00	Curtis 2015 (PSSRU), 10.4 Nurse specialist (community), including quals.
GP practice nurse - non-face-to-face contact (per hour)	£43.00	Curtis 2015 (PSSRU), 10.6 Nurse (GP practice), including qualifications
General practitioner (per hour)	£225.00	Curtis 2015 (PSSRU), 10.8b GP, including direct care staff costs, with quals.
Healthcare and admin staff inputs index case testing mutation positive cases (per person)	£396.24	Kerr 2017 (resource use Welsh FH service, unit costs PSSRU)
Healthcare and admin staff inputs index case testing mutation negative cases (per person)	£199.74	Kerr 2017 (resource use Welsh FH service, unit costs PSSRU)
Healthcare and admin staff inputs relative testing mutation positive cases (per person)	£279.07	Kerr 2017 (resource use Welsh FH service, unit costs PSSRU)
Healthcare and admin staff inputs relative testing mutation negative cases (per person)	£174.67	Kerr 2017 (resource use Welsh FH service, unit costs PSSRU)
Hospital nurse, band 7 (per hour) no patient contact	£60.00	Curtis 2015 (PSSRU), hospital-based nurse band 7
Hospital nurse, band 7 (per hour) patient contact	£131.00	Curtis 2015 (PSSRU), hospital-based nurse band 7
Consultant medical (per hour)	£182.21	Curtis 2015 (PSSRU), Consultant: medical, including qualifications * inflation for non face-to-face time from Curtis 2008 (PSSRU) - no newer data were available
Lipid clinic/hospital administration assistant	£24.00	Curtis 2015(PSSRU), Allied health professional support worker
Lipid profile	£3.05	CG181 indexed to 2016

The cost of treatment for people with FH was based on the proportion of people on high potency medicines from the Welsh, Scottish and Wessex FH services combined with unit costs from the NHS Drug Tariff (Table 10).[2,35] The proportion prescribed does not sum to 100% because some people take statins alone, some take ezetimibe alone, and some are prescribed both. The cost of events associated with cardiovascular disease were obtained from the NHS Reference Costs 2015-16 and summarised in the Supplementary Material. For the polygenic cohort, the cost of atorvastatin 20 mg was £1.04 per pack (Drug Tariff November 2016) resulting in a first year cost with monitoring of £129.09 and £111.06 for subsequent years.[35]

Table 10: Cost of lipid modification for FH

Dose	Cost per pack	Doses per pack	Cost per dose	Annual cost	% prescribed
Atorvastatin 80 mg	£1.89	28	£0.07	£24.65	70.77%
Rosuvastatin 40 mg	£29.69	28	£1.06	£387.30	15.53%
Ezetimibe 10 mg	£26.31	28	£0.94	£343.20	40.00%
Weighted average				£214.89	

Table 11: Cost of CVD events

PROCEDURES	Unit cost	Source of cost	Detail of source
1x GP appointment	£ 44.00	PSSRU 2015 (10.8b)	1 appointment: GP, 11.7 min, incl direct care staff costs and qualifications
1x GP Nurse appointment	£ 14.47	PSSRU 2015 (10.6)	1 appointment: GP practice nurse, 15.5 min, £52 per hour of face-to-face contact including qualifications
1x HCA appointment	£ 5.17	PSSRU 2015 (10.5)	1 appointment: Clinical support worker nursing (community), 15.5 min (based on nurse appointment length), £25 per hour of patient-related work
1x Cardiology initial appointment	£ 156.00	NHS Ref Costs 2015-16	WF01B Consultant led
1x Cardiology follow-up appointment	£ 122.00	NHS Ref Costs 2015-16	WF01A Consultant led
1x Cardiology follow-up non-consultant led (nurse)	£ 94.00	NHS Ref Costs 2015-16	WF01A Non-consultant led
Angina hospitalisation	£709.92	NHS Ref Costs 2015-16	Weighted average of EB13A-D
MI (suspected) hospitalisation	£1,497.47	NHS Ref Costs 2015-16	Weighted average of EB10A-E
(50%) TIA hospitalisation	£977.35	NHS Ref Costs 2015-16	Weighted average of AA29C-F
Stroke hospitalisation	£3,332.34	NHS Ref Costs 2015-16	Weighted average of AA35A-F
HF hospitalisation	£2,066.10	NHS Ref Costs 2015-16	Weighted average of EB03A-E
(10%) PAD hospitalisation	£1,808.69	NHS Ref Costs 2015-16	Weighted average of YQ50A-F
(60%) PCI elective	£2,320.92	NHS Ref Costs 2015-16	Weighted average of YR10A-C, YR11A-D: EI+EBD
(5%) PCI elective	£2,320.92	NHS Ref Costs 2015-16	Weighted average of YR10A-C, YR11A-D: EI+EBD
PPCI emergency	£7,396.07	NHS Ref Costs 2015-16	Weighted average of YR12Z, YR13Z, YR14A-B, YR15A-C: NEI+NEEBD, NESS

(40%) Non-coronary PI	£1,208.06	NHS Ref Costs 2015-16	Weighted average of YR23A-B, YR24C-D
(10%) Non-coronary PI	£1,208.06	NHS Ref Costs 2015-16	Weighted average of YR23A-B, YR24C-D
(25%) Complex echocardiogram	£253.04	NHS Ref Costs 2015-16	EY50Z
(40%) CABG	£10,875.62	NHS Ref Costs 2015-16	Weighted average of ED26A-C, ED27A-C, ED28A-C
(5%) CABG	£10,875.62	NHS Ref Costs 2015-16	Weighted average of ED26A-C, ED27A-C, ED28A-C
Angiography	£1,695.89	NHS Ref Costs 2015-16	Weighted average of EY43A-F
(50%) CT scan, one area	£138.75	NHS Ref Costs 2015-16	RD28Z Complex computerised tomography scan
Stroke rehab programme	£906.29	CG162 Stroke rehabilitation	Appendix K.2.3.5 p705, indexed to 2016

When 2015 PSSRU staff costs are used it is because 2016 costs were not available in the correct format. Based on other comparable data, the 2015 costs were thought not to have meaningfully changed, however.

When these unit costs are combined with the probability of those costs occurring (from the decision tree), we derive the expected cost per person for that strategy (Table 43).

Table 12: Expected short term costs per person per subpopulation

Total cost of each strategy, adjusted for the probability of individual resource use		
1. No case identification or cascade testing		
No cost incurred in identification and diagnosis module	£0.00	
2. Cascade testing		
People with a current clinical diagnosis of FH		
Genetic test for index case	£375.00	UK Genetic Testing Network website
Healthcare and admin staff inputs index case testing mutation positive cases	£396.24	Kerr 2016 (resource use Welsh FH service, unit costs PSSRU)
Healthcare and admin staff inputs index case testing mutation negative cases	£199.74	Kerr 2016 (resource use Welsh FH service, unit costs PSSRU)
Expected cost	£521.33	
Relatives of people with a current clinical diagnosis of FH		
Offer cascade testing regardless of acceptance (all contacted relatives)	£18.75	15 minutes nurse specialist
Genetic test for relative where FH mutation is known	£117.50	UK Genetic Testing Network website
Healthcare and admin staff inputs relative testing mutation positive cases	£279.07	Kerr 2016 (resource use Welsh FH service, unit costs PSSRU)

Healthcare and admin staff inputs relative testing mutation negative cases	£174.67	Kerr 2016 (resource use Welsh FH service, unit costs PSSRU)
Lipid profile for relatives that accept cascade testing	£3.05	CG181 lipid modification model indexed to 2015
Expected cost	£191.22	
3. Primary care case identification and clinical assessment with SB		
People with a current clinical diagnosis of FH		
As per strategy 2	£521.33	
Relatives of people with a current clinical diagnosis of FH		
As per strategy 2	£191.22	
People identified by primary care database search (potential new index cases)		
Informatics setup and introduction session per at risk patient	£17.13	1 hour of 2 GPs and 2 GP practice nurses ÷ 31 (6127 patients per practice x 0.51% (Futema 2015 TC >9.3))
Information gathering (for all patients identified by search)	£10.75	15 minutes GP practice nurse non-face-to-face
Clinical assessment for those that accept using Simon Broome criteria	£18.75	15 minutes nurse specialist
GP consultation for referral to lipid clinic	£56.25	15 minutes GP
Information pack for those that accept clinical assessment	£2.00	assumed
Genetic test for index case	£375.00	UK Genetic Testing Network website
Lipid clinic healthcare and admin staff inputs index case testing mutation positive cases	£396.24	Kerr 2016
Lipid clinic healthcare and admin staff inputs index case testing mutation negative cases	£199.74	Kerr 2016
Lipid profile (GP) for those that accept clinical assessment	£3.05	CG181 lipid modification model indexed to 2015
Expected cost	£172.07	
Relatives of people with FH identified through primary care database search		
Offer cascade testing regardless of acceptance (all contacted relatives)	£18.75	15 minutes nurse specialist
Genetic test for relative where FH mutation is known	£117.50	UK Genetic Testing Network website
Healthcare and admin staff inputs relative testing mutation positive cases	£279.07	Kerr 2016 (resource use Welsh FH service, unit costs PSSRU)
Healthcare and admin staff inputs relative testing mutation negative cases	£174.67	Kerr 2016 (resource use Welsh FH service, unit costs PSSRU)
Lipid profile for those that accept genetic testing	£3.05	CG181 lipid modification model indexed to 2015
Expected cost	£52.68	
4. Primary care case identification and clinical assessment with DLCN		

People with a current clinical diagnosis of FH		
As per strategy 2	£521.33	
Relatives of people with a current clinical diagnosis of FH		
As per strategy 2	£191.22	
People identified by primary care database search (potential new index cases)		
Informatics setup and introduction session per at risk patient	£17.13	1 hour of 2 GPs and 2 GP practice nurses ÷ 31 (6127 patients per practice x 0.51% (Futema 2015 TC >9.3))
Information gathering (for all patients identified by search)	£10.75	15 minutes GP practice nurse non-face-to-face
Clinical assessment for those that accept using DLCN criteria	£37.50	30 minutes specialist nurse
GP consultation for referral to lipid clinic	£56.25	15 minutes GP
Information pack for those that accept clinical assessment	£2.00	assumed
Genetic test for potential new index case	£375.00	UK Genetic Testing Network website
Healthcare and admin staff inputs index case testing mutation positive cases	£396.24	Kerr 2016
Healthcare and admin staff inputs index case testing mutation negative cases	£199.74	Kerr 2016
Lipid profile for those that accept clinical assessment	£3.05	CG181 lipid modification model indexed to 2015
Expected cost	£155.26	
Relatives of people with FH identified through primary care database search		
Offer cascade testing regardless of acceptance (all contacted relatives)	£18.75	15 minutes nurse specialist
Genetic test for relative where FH mutation is known	£117.50	UK Genetic Testing Network website
Healthcare and admin staff inputs relative testing mutation positive cases	£279.07	Kerr 2016 (resource use Welsh FH service, unit costs PSSRU)
Healthcare and admin staff inputs relative testing mutation negative cases	£174.67	Kerr 2016 (resource use Welsh FH service, unit costs PSSRU)
Lipid profile for those that accept genetic testing	£3.05	CG181 lipid modification model indexed to 2015
Expected cost	£50.96	
5. Secondary care case identification and clinical assessment with SB		
People with a current clinical diagnosis of FH		
As per strategy 2	£521.33	
Relatives of people with a current clinical diagnosis of FH		
As per strategy 2	£191.22	

People with early MI (potential new index cases)		
Information gathering and invitation for further clinical assessment (all patients with early MI)	£15.00	15 minutes hospital-based nurse band 7, no patient contact
Clinical assessment using SB criteria	£32.75	15 minutes hospital-based nurse band 7, patient contact
Information pack with clinical assessment	£2.00	assume
Genetic test for potential new index case	£375.00	UK Genetic Testing Network website
Healthcare and admin staff inputs index case testing mutation positive cases	£396.24	Kerr 2016
Healthcare and admin staff inputs index case testing mutation negative cases	£199.74	Kerr 2016
Expected cost	£339.90	
Relatives of people with FH who have had early MI		
Offer cascade testing regardless of acceptance (all contacted relatives)	£32.75	15 minutes hospital-based nurse band 7, patient contact
Genetic test for relative where FH mutation is known	£117.50	UK Genetic Testing Network website
Healthcare and admin staff inputs relative testing mutation positive cases	£279.07	Kerr 2016 (resource use Welsh FH service, unit costs PSSRU)
Healthcare and admin staff inputs relative testing mutation negative cases	£174.67	Kerr 2016 (resource use Welsh FH service, unit costs PSSRU)
Lipid profile for those that accept genetic testing	£3.05	CG181 lipid modification model indexed to 2015
Expected cost	£155.75	

6. Secondary care case identification and clinical assessment with DLCN

People with a current clinical diagnosis of FH		
As per strategy 2	£521.33	
Relatives of people with a current clinical diagnosis of FH		
As per strategy 2	£191.22	
People with early MI (potential new index cases)		
Information gathering and invitation for further clinical assessment (all patients with early MI)	£15.00	15 minutes hospital-based nurse band 7, no patient contact
Clinical assessment using DLCN criteria	£65.50	30 minutes hospital-based nurse band 7, patient contact
Information pack with clinical assessment	£2.00	assume
Genetic test for potential new index case	£375.00	UK Genetic Testing Network website
Healthcare and admin staff inputs index case testing mutation positive cases	£396.24	Kerr 2016
Healthcare and admin staff inputs index case testing mutation negative cases	£199.74	Kerr 2016
Expected cost	£293.51	

Relatives of people with FH who have had early MI		
Offer cascade testing regardless of acceptance (all contacted relatives)	£32.75	15 minutes hospital-based nurse band 7, patient contact
Genetic test for relative where FH mutation is known	£117.50	UK Genetic Testing Network website
Healthcare and admin staff inputs relative testing mutation positive cases	£279.07	Kerr 2016 (resource use Welsh FH service, unit costs PSSRU)
Healthcare and admin staff inputs relative testing mutation negative cases	£174.67	Kerr 2016 (resource use Welsh FH service, unit costs PSSRU)
Lipid profile for those that accept genetic testing	£3.05	CG181 lipid modification model indexed to 2015
Expected cost	£150.67	

7. Primary care and secondary care case identification with SB criteria

People with a current clinical diagnosis of FH		
As per strategy 2	£521.33	
Relatives of people with a current clinical diagnosis of FH		
As per strategy 2	£191.22	
People identified by primary care database search (potential new index cases)		
As per strategy 3	£172.23	
Relatives of people with FH identified through primary care database search		
As per strategy 3	£52.68	
People with early MI (potential new index cases)		
As per strategy 5	£339.90	
Relatives of people with FH who have had early MI		
As per strategy 5	£155.75	

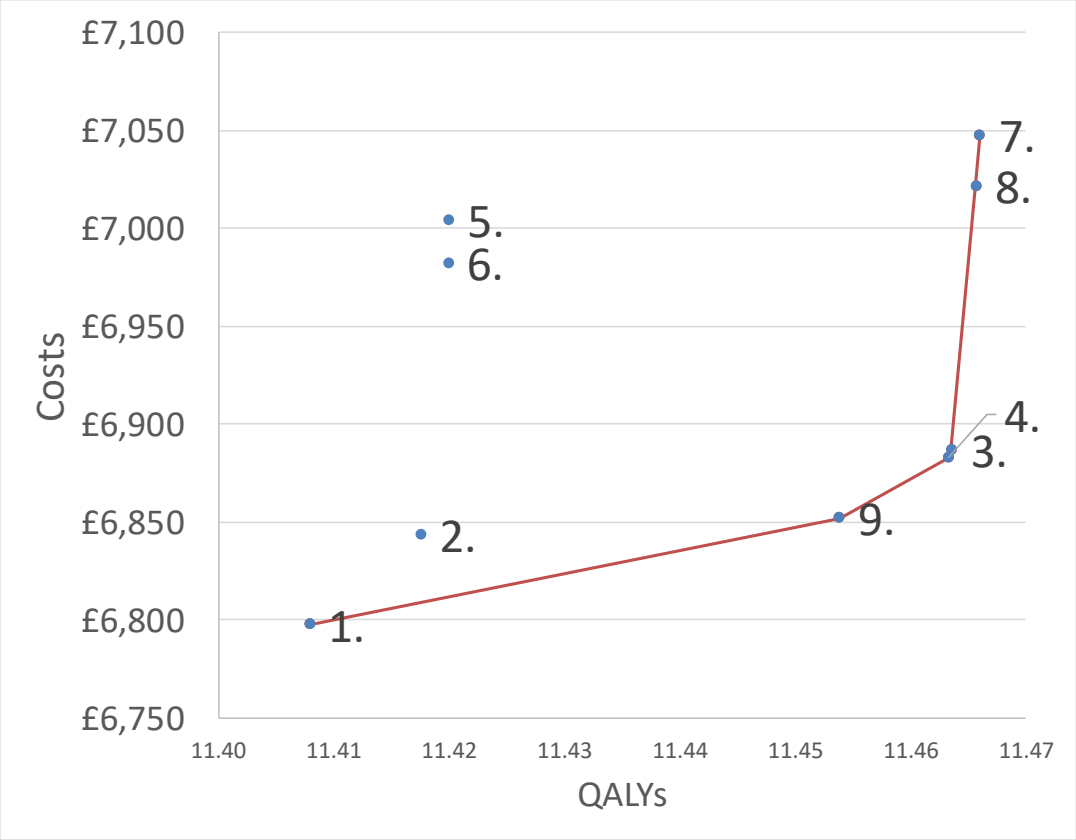
8. Primary care and secondary care case identification with DLCN criteria

People with a current clinical diagnosis of FH		
As per strategy 2	£521.33	
Relatives of people with a current clinical diagnosis of FH		
As per strategy 2	£191.22	
People identified by primary care database search (potential new index cases)		

As per strategy 4	£155.26	
Relatives of people with FH identified through primary care database search		
As per strategy 4	£50.96	
People with early MI (potential new index cases)		
As per strategy 6	£293.51	
Relatives of people with FH who have had early MI		
As per strategy 6	£150.67	
9. Primary care case identification with DLCN criteria, cascade testing currently diagnosed only (not relatives of new index cases) (used for sensitivity analysis only - see section O.4.3)		
People with a current clinical diagnosis of FH		
As per strategy 2	£521.33	
Relatives of people with a current clinical diagnosis of FH		
As per strategy 2	£191.22	
People identified by primary care database search (potential new index cases)		
Informatics setup and introduction session per at risk patient	£17.13	1 hour of 2 GPs and 2 GP practice nurses ÷ 31 (6127 patients per practice x 0.51% (Futema 2015 TC >9.3))
Information gathering (for all patients identified by search)	£10.75	15 minutes GP practice nurse non-face-to-face
GP consultation for those that accept	£56.25	15 minutes GP
Lipid profile for those that accept	£3.05	CG181 lipid modification model indexed to 2015
Expected cost	£43.48	
Relatives of people with FH identified through primary care database search		
No intervention	£0.00	
People with early MI (potential new index cases)		
No intervention	£0.00	
Relatives of people with FH who have had early MI		
No intervention	£0.00	

10 Results: cost-effectiveness plane, base case

Figure 1: Cost-effectiveness plane and frontier, base case



11 Results of one way sensitivity analysis

One way sensitivity analysis - prevalence of FH

	General population		Identified by primary care database search		People with early MI	
Strategy	**Low**	**High**	**Low**	**High**	**Low**	**High**
Amounts >	**0.20%**	**0.46%**	**15.00%**	**41.18%**	**0.30%**	**8.30%**
1. No cascade testing and no case identification	8	8	8	8	7	8
2. Cascade testing	5	5	5	5	5	7
3. Primary care case identification, clinical assessment with SB criteria	1	1	2	1	1	3
4. Primary care case identification, clinical assessment with DLCN criteria	2	2	1	2	2	4
5. Secondary care case identification, clinical assessment with SB criteria	7	7	7	7	8	6
6. Secondary care case identification, clinical assessment with DLCN criteria	6	6	6	6	6	5
7. Primary and secondary care case identification, clinical assessment with SB criteria	4	4	4	4	4	2
8. Primary and secondary care case identification, clinical assessment with DLCN criteria	3	3	3	3	3	1

One way sensitivity analysis - take up

	Current clinical diagnosis of FH		Identified by primary care database search		Early MI		Relatives of current clinical diagnosis		Relatives of new primary care index cases		Relatives of new secondary care index cases	
Strategy	**Low**	**High**	**Low**	**High**	**Low**	**High**	**Low**	**High**	**Low**	**High**	**Low**	**High**
Amount >	**69.10%**	**98.90%**	**13.00%**	**50.00%**	**54.38%**	**90.63%**	**44.92%**	**74.86%**	**44.92%**	**74.86%**	**44.92%**	**74.86%**
1. No cascade testing and no case identification	7	8	8	8	8	7	6	8	8	8	8	8
2. Cascade testing	5	5	5	5	5	5	5	5	5	5	5	5
3. Primary care case identification, clinical assessment with SB criteria	1	1	1	1	1	1	1	1	1	1	1	1
4. Primary care case identification, clinical assessment with DLCN criteria	2	2	2	2	2	2	2	2	2	2	2	2

5. Secondary care case identification, clinical assessment with SB criteria	8	7	7	7	7	8	8	7	7	7	7	7
6. Secondary care case identification, clinical assessment with DLCN criteria	6	6	6	6	6	6	7	6	6	6	6	6
7. Primary and secondary care case identification, clinical assessment with SB criteria	4	4	4	4	4	4	4	4	4	4	4	4
8. Primary and secondary care case identification, clinical assessment with DLCN criteria	3	3	3	3	3	3	3	3	3	3	3	3

One way sensitivity analysis - number of relatives and cost of genetic testing

	Number of relatives		Cost of genetic testing	
Strategy	**Low**	**High**	**Low**	**High**
Amount >	**1**	**12**	**£287.00**	**£460.00**
1. No cascade testing and no case identification	6	8	8	7
2. Cascade testing	5	7	5	5
3. Primary care case identification, clinical assessment with SB criteria	2	3	1	1
4. Primary care case identification, clinical assessment with DLCN criteria	1	4	2	2
5. Secondary care case identification, clinical assessment with SB criteria	8	6	7	8
6. Secondary care case identification, clinical assessment with DLCN criteria	7	5	6	6
7. Primary and secondary care case identification, clinical assessment with SB criteria	4	1	4	4
8. Primary and secondary care case identification, clinical assessment with DLCN criteria	3	2	3	3

One way sensitivity analysis - clinical assessment as 'rule in' test

	Clinical assessment profile
Strategy	Primary & secondary
Amount >	Definite only
1. No cascade testing and no case identification	8
2. Cascade testing	5
3. Primary care case identification, clinical assessment with SB criteria	2
4. Primary care case identification, clinical assessment with DLCN criteria	1
5. Secondary care case identification, clinical assessment with SB criteria	6
6. Secondary care case identification, clinical assessment with DLCN criteria	7
7. Primary and secondary care case identification, clinical assessment with SB criteria	3
8. Primary and secondary care case identification, clinical assessment with DLCN criteria	4

One way sensitivity analysis - QRISK

	Proportion assigned to risk bands		
Strategy	QRISK		
Amount >	30%	20%	10%
1. No cascade testing and no case identification	8	8	6
2. Cascade testing	5	5	5
3. Primary care case identification, clinical assessment with SB criteria	1	1	1
4. Primary care case identification, clinical assessment with DLCN criteria	2	2	2
5. Secondary care case identification, clinical assessment with SB criteria	7	7	8
6. Secondary care case identification, clinical assessment with DLCN criteria	6	6	7

7. Primary and secondary care case identification, clinical assessment with SB criteria	4	4	4
8. Primary and secondary care case identification, clinical assessment with DLCN criteria	3	3	3

One way sensitivity analysis - Proportion already on statins

	Proportion of People Already taking Statins								
Strategy									
Amount >	**19%**	**30%**	**40%**	**50%**	**60%**	**70%**	**80%**	**99%**	**10%**
1. No cascade testing and no case identification	8	8	8	8	8	8	8	8	8
2. Cascade testing	5	5	5	5	5	5	5	5	5
3. Primary care case identification, clinical assessment with SB criteria	1	1	1	1	1	1	1	1	1
4. Primary care case identification, clinical assessment with DLCN criteria	2	2	2	2	2	2	2	2	2
5. Secondary care case identification, clinical assessment with SB criteria	7	7	7	7	7	7	7	7	7
6. Secondary care case identification, clinical assessment with DLCN criteria	6	6	6	6	6	6	6	6	6
7. Primary and secondary care case identification, clinical assessment with SB criteria	4	4	4	4	4	4	4	4	4
8. Primary and secondary care case identification, clinical assessment with DLCN criteria	3	3	3	3	3	3	3	3	3

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