National Institute for Health and Care Excellence

Final

Familial hypercholesterolaemia: identification and management

Evidence reviews for case-finding, diagnosis and statin monotherapy

NICE guideline CG71

Evidence reviews

[November 2017]

December 2017: The definition of high-intensity statin was amended to: Statins are classified as high intensity if they produce average reductions in LDL-C greater than 40%. See appendix A of the NICE guideline on cardiovascular disease: risk assessment and reduction, including lipid modification.

See https://www.nice.org.uk/guidance/cg181/chapter/appendix-a-grouping-of-statins for more details.

Final

These evidence reviews were developed by NICE's Guideline Updates Team

Disclaimer

Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and, where appropriate, their guardian or carer.

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Contents

Clinical guidelines update

The NICE clinical guidelines update team update discrete parts of published clinical guidelines as requested by NICE's Guidance Executive.

Suitable topics for update are identified through the surveillance programme (see surveillance programme interim guide).

These guidelines are updated using a standing committee of healthcare professionals, research methodologists and lay members from a range of disciplines and localities. For the duration of the update the 5 core standing members of the committee are usually joined by up to 5 condition specific standing members and by a further 5 additional members who are have specific expertise in the topic being updated, hereafter referred to as 'topic expert members'.

In this document where 'the committee' is referred to, this means the entire committee, both the standing members and topic expert members.

Where 'standing committee members' is referred to, this means the core standing members of the committee only.

Where 'topic expert members' is referred to this means the recruited group of members with topic expertise.

Where 'condition specific standing members' are referred to, this means the condition specific standing members of the committee only.

All of the standing members and the topic expert members are fully voting members of the committee.

Details of the committee membership and the NICE team can be found in Appendix A:. The committee members' declarations of interest can be found via Appendix B:.

1 Summary section

1.1 Update information

The NICE guideline on familial hypercholesterolaemia (NICE clinical guideline CG71) was reviewed in June 2015 as part of NICE's routine surveillance programme to decide whether it required updating. The surveillance report identified new evidence relating to the use of different methods for the identification of familial hypercholesterolaemia (FH), updated methods for diagnosing FH and more information on the cost effectiveness of statins in the treatment of FH.

The full surveillance report can be found here.

Some recommendations can be made with more certainty than others. The committee makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the committee is confident that, given the information it has looked at, most people would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

For all recommendations, NICE expects that there is discussion with the person about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision (see also 'Patient-centred care').

Recommendations that must (or must not) be followed

We usually use 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally we use 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Recommendations that should (or should not) be followed– a 'strong' recommendation

We use 'offer' (and similar words such as 'refer' or 'advise') when we are confident that, for the vast majority of people, following a recommendation will do more good than harm, and be cost effective. We use similar forms of words (for example, 'Do not offer…') when we are confident that actions will not be of benefit for most people.

Recommendations that could be followed

We use 'consider' when we are confident that following a recommendation will do more good than harm for most people, and be cost effective, but other options may be similarly cost effective. The course of action is more likely to depend on the person's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the person.

1.2 Recommendations

1. **Suspect familial hypercholesterolaemia (FH) as a possible diagnosis in adults with:**
    - a total cholesterol level greater than 7.5 mmol/l **and/or**
    - a personal or family history of premature coronary heart disease[1] (an event before 60 years in an index individual or first-degree relative). **[2008, amended 2017]**

2. **Systematically search primary care records for people:**
    - younger than 30 years, with a total cholesterol concentration greater than 7.5 mmol/l **and**
    - 30 years or older, with a total cholesterol concentration greater than 9.0 mmol/l

as these are the people who are at highest risk of FH. [2017]

3. **For people with a personal or family history of premature coronary heart disease[1] (an event before 60 years in an index individual or first-degree relative), but whose total cholesterol is unknown, offer to measure their total cholesterol. [2017]**

4. **Carry out cascade testing using DNA testing to identify affected first-and second-and, when possible, third-degree biological relatives of people with a genetic diagnosis of FH. [2017]**

5. **In children aged 0-10 years at risk of FH because of one affected parent, offer a DNA test at the earliest opportunity. If testing of a child at risk has not been undertaken by the age of 10 years, offer an additional opportunity for a DNA test. [2017]**

6. **Use the Simon Broome or Dutch Lipid Clinic Network (DLCN) criteria to make a clinical diagnosis of FH in primary care settings. This should be done by a healthcare professional competent in using the criteria. [2017]**

7. **Refer the person to an FH specialist service for DNA testing if they meet the Simon Broome criteria for possible or definite FH, or they have a DLCN score greater than 5. [2017]**

8. **Inform all people who have an identified mutation diagnostic of FH that they have an unequivocal diagnosis of FH even if their LDL-C concentration does not meet the diagnostic criteria (see recommendation 6). [2008, amended 2017]**

9. **Offer a high-intensity statin with the lowest acquistion cost as the initial treatment for all adults with FH and aim for at least a 50% reduction in LDL-C concentration from the baseline measurement. [2017]**

10. **Offer statins to children with FH by the age of 10 years or at the earliest opportunity thereafter. [2017]**

11. **For children and young people with FH, consider a statin that is licensed for use in the appropriate age group. [2017]**

12. **Statin therapy for children and young people should be initiated by a healthcare professional with expertise in treating children and young people with FH, and in a child-focused setting. [2008, amended 2017]**

13. **Coronary heart disease risk estimation tools, such as QRISK2 and those based on the Framingham algorithm, should not be used because people with FH are already at a high risk of premature coronary heart disease. [2008, amended 2017]**

1.3 Patient-centred care

This guideline offers best practice advice on the care of people with familial hypercholesterolaemia.

People have the right to be involved in discussions and make informed decisions about their care, as described in your care.

NICE has also produced guidance on the components of good patient experience in adult NHS services. All healthcare professionals should follow the recommendations in Patient experience in adult NHS services.

1.4 Methods

This update was developed based on the process and methods described in the Developing NICE guidelines: the manual. Specific methods used in addressing each question are detailed in the respective evidence reviews and review protocols.

[1] angina, acute coronary syndrome, myocardial infarction, need for coronary artery bypass grafting, need for percutaneous coronary intervention and/or definite coronary artery disease on coronary angiography

2 Evidence review and recommendations: case-finding

2.1 Introduction

Familial Hypercholesterolaemia (FH) is characterised by an inherited genetic defect (or mutation) which causes a high cholesterol concentration from birth. This may lead to early development of atherosclerosis and coronary heart disease. Familial hypercholesterolaemia has an autosomal dominant pattern of inheritance; siblings and children of people with FH have a 50% risk of inheriting FH.

The combination of tests used to identify individuals with FH depends upon whether the diagnosis is of an individual with FH from a registry or database or identifying FH in relatives of an individual with FH (also known as index case) through cascade testing. Cascade testing is a mechanism for identifying people at risk of a genetic condition by a process of family tracing. Cascade testing can be direct or indirect: Direct cascade testing is where a healthcare professional makes direct contact with the relatives of the index case already diagnosed with (or identified as having) FH; indirect cascade testing is where the index case contacts their own relatives themselves.

Diagnosis of FH in an index individual can be based on the Simon Broome criteria, Dutch Lipid Network Criteria, MEDPED or LDL-cholesterol concentration. In families in which a mutation has been identified, the mutation and not LDL-C concentration should be used to identify affected relatives. Diagnosis of FH in a relative of the index case where a family mutation has not been identified is based on gender and age specific LDL-C criteria, (Appendix F of CG71). Identification by cholesterol levels alone is not always accurate and therefore DNA testing is the gold standard for identification of FH.

Evidence from the surveillance review suggested that cascade testing may now be more cost-effective than stated in the original guideline. The predicted improvement in cost effectiveness may be due to atorvastatin coming off patent, reduced costs of DNA testing and more people with FH being cared for in the community. It has been identified that the prevalence of FH appears to be higher than commonly reported, implying that there is even more under-diagnosis and under-treatment than previously thought, which in turn may have led to an underestimation of the benefits of cascade testing in the original guideline.

Cascade testing was recommended in the original guideline and was cost effective, but was not widely implemented. Therefore, there may now be other strategies which are more efficient and cost effective, and the evidence on this should be updated.

2.2 Review question

What is the clinical and cost-effectiveness of using the following strategies for identifying people with FH through:

- Primary care electronic databases to identify people with
  - history of early myocardial infarction (MI) (<60 years) and hypercholesterolemia
  - family history of ischemic heart disease and hypercholesterolemia or;
- Secondary care electronic databases
  - within cardiac care facilities or cardiac investigation units to identify people with history of early MI (<60 years) and hypercholesterolemia or

- within pathology departments to identify people through pathology databases with history of early MI (<60 years) and hypercholesterolemia
- Direct and Indirect cascade testing (including reverse cascade testing)?

2.3 Clinical evidence review

2.3.1 Methods

This review was conducted according to the process outlined in the review protocol (see Appendix C.2), with the following exceptions:

Results

The results for diagnostic yield were reported as median values because the data was expected not to be normally distributed. Where 3 or more studies reported a diagnostic yield median and range were reported; where 2 studies reported diagnostic yield, only the range was reported. Where only a single study reported the diagnostic yield, the single outcome from that study is reported in the modified GRADE table and evidence statements. Where uptake rate is reported, the numerator is the number of people who underwent assessment or testing for FH, and the denominator is the number of people who were offered the opportunity to be tested for FH.

Quality assessment

As prospective or retrospective cohort studies were considered the most appropriate study types to answer this review question, the modified GRADE quality rating started at “high”, and was downgraded for any concerns about risk of bias (according to CASP cohort checklist), indirectness, inconsistency or imprecision (as detailed in the review protocol, appendix C1). Where case-series studies were included the quality rating started at very low. Imprecision could not be quantitatively assessed as only median and range values were reported; all outcomes were downgraded one level for imprecision due to the uncertainty caused by not being able to assess precision directly.

2.3.2 Results

A systematic search was conducted (see Appendix D.1) which identified 10,010 articles. The titles and abstracts were screened and 104 articles were identified as potentially relevant. Full-text versions of these articles were ordered and reviewed against the criteria specified in the review protocol (see Appendix C.1). Of these, 64 were excluded as they did not meet the criteria and 40 studies (from 41 references) met the criteria and were included. Due to the publication of a study key to the review, an update search was undertaken to ensure the review was as up to date as possible. The update search retrieved 1,002 articles. The titles and abstracts were screened and 15 articles were identified as potentially relevant. Full-text versions of these articles were ordered and reviewed against the criteria specified in the review protocol (Appendix C.1). Of these, 12 were excluded as they did not meet the criteria and 3 studies met the criteria and were included. This resulted in a total of 43 included studies from 44 publications.

A review flowchart is provided in Appendix E.1, and the excluded studies (with reasons for exclusion) are shown in Appendix F.1. The included studies were categorised as follows:

- Fourteen studies assessed cascade testing (7 used direct cascade testing only, 2 used indirect cascade testing only, 2 studies used a combination of both, and 3 did not report the specific method used),
- Seven studies assessed primary care electronic database searching and
- Twenty-two studies assessed secondary care electronic database searching.

There was variation in the methods used in each study to detect FH. Criteria used included:

- Simon Broome criteria,
- Medped criteria
- Dutch Lipid Clinic Network (DLCN) Criteria and
- DNA/molecular diagnosis.

Studies which used DNA diagnosis differed in their methods of DNA testing and the mutations analysed. We only included studies of DNA testing if the DNA tests were for LDLR, APOB and PCSK9 mutations.

The committee made a post-hoc decision that the interventions included in the primary care studies (n= 8) were too disparate to be pooled as they included a variety of database searching methodologies and differed in the diagnostic criteria for FH (and validation of those criteria). Therefore the evidence for this part of the review is presented in a narrative summary format.

The committee also decided that the secondary care sources should be classed into distinct categories as follows:

- Pathology databases,
- Lipid clinics/registries,
- Coronary care units/Myocardial Ischaemia National Audit Project (MINAP) and
- Screening programs

For a summary of the included studies please see Table 1, Table 2, Table 3 & Table 7 (for the full evidence tables and full GRADE profiles please see appendices G.1 and H.1).

Table 1 Summary of included studies: Cascade testing

Study reference (including study design)	Study population	Method	Outcomes reported	Comments
Bell 2015	366 relatives of 100 index patients	Genetic cascade testing -direct	Diagnostic yield	
Bhatnager 2000	259 probands + 285 1st degree relatives	Cascade screening -direct	Diagnostic yield	Included in CG71
Hadfield 2009	931 index cases, 2,292 living first degree relatives	Cascade testing – direct and indirect	Diagnostic yield	
Jannes 2015	248 index patients, 394 relatives	Cascade testing – direct and indirect	Diagnostic yield Sensitivity and specificity of genetic vs DLCN and SB.	
Lee 1998	80 index patients and 200 relatives of probands, 50 controls	Cascade testing – method not reported	Diagnostic yield	
Leren 2008	2,472 relatives of 440 index patients	Cascade testing - indirect	Diagnostic yield Sensitivity and specificity of GP diagnosis of FH	

Study reference (including study design)	Study population	Method	Outcomes reported	Comments
Marks 2006	227 index cases, 1,075 first degree relatives	Cascade testing - indirect	Diagnostic yield	Included in CG71
Muir 2010	353 relatives of 76 index cases + 95 people with a severe phenotype but no identified mutation	Cascade testing-Direct	Diagnostic yield	
Taylor 1993	200 children	Cascade testing – direct	Diagnostic yield	
Thorsson 2003	2,201 living individuals in 4 family clusters	Cascade testing – direct	Diagnostic yield	Undertaken in Iceland, limited applicability in UK setting due to method of family tracing
Umans-Eckenhausen 2002	1,695 relatives of 66 consecutive index patients	Cascade testing – direct	Diagnostic yield	Only relatives of index cases included in study.
Umans-Eckenhausen 2001	5,442	Cascade testing using secondary care lipid clinic databases-direct	Diagnostic yield Referral for treatment	Included in CG71 Relatives of 237 people
Van Maarle 2002	677 consecutive patients	Cascade testing – direct	Diagnostic yield	
Vergotine 2001	790	Cascade testing-method not reported	Diagnostic yield	Relatives of 379 index cases

Table 2: Summary of included studies: Primary care electronic database

Study reference (including study design)	Study population	Method	Outcomes reported	Comments
Bell 2014b	153	Primary care	Diagnostic yield	
Gray 2008	12,100	Primary care database	Sensitivity Diagnostic yield	Included in CG71
Green 2016	Approximately 290,000	Primary care database searching	Diagnostic yield	Patients registered with a GP
Kirke 2015	2,762	GP and workplace assessment	Diagnostic yield	Also recruited population from pathology database; please see secondary care section for this information.
Norsworthy 2014	617	Generation Scotland: Scottish family health study	Diagnostic yield	Primary health care data used. Database study (all others are primary research).

Study reference (including study design)	Study population	Method	Outcomes reported	Comments
Qureshi 2016	821	Primary care; education of practice staff, electronic prompts and mail out	Diagnostic yield	Feasibility study. Also includes information on number of referrals to secondary care specialist
Troeung 2016	3,708	Primary care database	Diagnostic yield	Comparison of electronic screening with GP manual search of records.

Primary care narrative review

One study based in Australia identified people at risk of having FH (either identified as having an elevated LDL-C level or identified from a GP database (using an unknown informatics tool - search strategy not reported); From a total of 153 people identified as at high risk, a specialist identified 45 people as having clinical FH using DLCN criteria (≥6 [probable or definite]), and the GP identified 39 people as having clinical FH using DLCN criteria, representing a diagnostic yield of 29.4% (number needed to test [nnt=4]) for the specialist and 25.5% (nnt=4) for the GP. A subset of 30 people with DLCN ≥4 (from the 45 originally assessed by the lipid specialist using primary care data) underwent genetic testing for FH: 4 individuals were mutation positive, a diagnostic yield of 7.5% (nnt =8). The evidence was of low quality; the quality was downgraded due to the lack of detail about the informatics tool and search terms used within the GP database to identify people at risk of having FH and at what concentration of LDL-C was considered elevated. There was also no detail about the population of the GP database, so the diagnostic yield within the population could not be calculated.

One study using a UK GP database with 12,100 people, searched computer records and notes (using key terms -read codes for IHD, lipid disorders and a search for statin and cholesterol >7.0 mmol/L) and identified 402 people with potential FH and a DLCN score was calculated for all those identified. The diagnostic yield from computer searches was 3.32% (nnt= 31). A GP and lipidologist manually viewed the data, notes and scores for each of the 402 patients; 12 were diagnosed with definite FH (diagnostic yield 2.99%, nnt= 34), 8 were diagnosed with probable FH (diagnostic yield 1.99%, nnt= 51), and 47 as being possible FH (diagnostic yield 11.69%, nnt= 9). The evidence was of low quality for the following reasons: no DNA testing was undertaken to confirm FH, therefore the diagnoses made using DLCN were not verified. Furthermore, the computer searches were undertaken using Read codes as search terms for IHD, lipid disorders, prescription for statins and cholesterol >7.0 mmol/L.

One study using UK GP databases within Medway clinical commissioning group with approximately 199,000 people, searched computer records (using Audit+ software an FH audit tool developed and based on recommendations from CG71) people with elevated TC or LDL-C (defined as TC>7.5mmol/L or LDL-C >4.9mmol/L) were flagged. The GP received electronic prompts to consider FH diagnosis when the person next attended the clinic: This stage of the study identified 99 people with clinical FH according to Simon Broome criteria for possible FH, representing a diagnostic yield of 0.05% and nnt=2013. In the second part of the study, a nurse assessed those people at risk identified by the initial computer search, but who had not been assessed by a GP:(those with elevated TC and LDL-C but who had not been assessed by Simon Broome criteria). The records of 1,505 patients were reviewed and 334 were diagnosed with FH (diagnostic yield 22.2%, nnt= 5 in a targeted population): 192 with definite FH, DLCN >8 (diagnostic yield 12.8%, nnt= 8), 83 with probable FH, DLCN 6-8 (diagnostic yield 5.5%, nnt=

18) and 59 with possible FH, DLCN 3-5 (diagnostic yield 3.9%, nnt= 25). The evidence was of low quality due to the fact that no DNA testing was undertaken to confirm genetic diagnosis of FH. In addition, those people identified as having FH through the Audit+ tool, only received a diagnosis of possible FH according to SB criteria, no further verification of the diagnosis was described.

One study undertaken in Australia with 42,179 people using a GP practice register and workplace screening. People in the workplace completed a 5 question screening questionnaire to assess their CAD risk[2]. Participation was voluntary and people who identified 2 or more positive risk factors were contacted by the research nurse and offered a primary care assessment. GP database screening involved screening the electronic records of 2 private GP practices using the Canning tool (data extraction software). Criteria were: age 18-70, history of cardiac event <60 years, any CAD, diagnosis of lipid disorder, TC >7.5 mmol/L, LDL >4.0mmol/L or prescription for statins. Of the 42,179 people included 2,762 were invited for testing and 1,259 were assessed for FH (uptake rate of 45.6%). 35 of those tested were categorised as high risk of FH (DLCN score of >5, calculated by research nurse in face-face assessment); the diagnostic yield within the population was 0.083% (nnt= 1,205) and the diagnostic yield within the people tested was 2.77% (nnt= 36). 29 people (out of 35, uptake rate of 82.8%) went on the have DNA testing for FH; 3 people were positive for FH causing mutations (diagnostic yield 10.34%, nnt= 10). The evidence was of low quality because people in the workplace screening section of the study were volunteers and therefore this part of the study was susceptible to selection bias.

One study undertaken in Scotland with 23,960 people where primary care databases were searched for people on the basis of TC and age thresholds (TC≥8mmol/L, any age; TC 8-8.4mmol/L, aged ≤50; 7-7.9mmol/L, age ≤40; TC≥5.5mmol/L; TC 5.1-5.2 mmol/L) : 617 people were identified from these searches and were divided into 3 groups: high cholesterol (TC ≥7mmol/L untreated), cholesterol therapy group (TC ≥5mmol/L and on lipid lowering therapy) and controls (people with TC 5.1-5.2 mmol/L). These 617 people underwent genetic testing and 9 people had FH diagnosed (mutations in one of the 3 genes (LDLR, APOB, PCSK9), representing a diagnostic yield of 1.46% (nnt= 69). This study was of very low quality; this was a database study, not primary research and the population of this study was older (aged 35-65 years) at recruitment. LDL-C concentration were not routinely collected, so recruitment was on the basis of TC and age only; this may identify a broader population of people than those truly at risk of FH.

In one study with 3,708 people based in Australia an informatics tool (TARB-Ex) that identified components to calculate a DLCN score (TC and LDL-C concentration, statin prescription, family history and clinical history), was used to assess all active medical records retrospectively for risk of FH. Those identified at risk of FH (DLCN ≥5) through TARB-Ex were assessed by a GP and lipid specialist. This was compared against manual review of a subset of 360 patient records (those with high lipid level (TC ≥7.0mmol/L or LDL-C ≥4.0mmol/L) and on statin treatment at time of highest LDL-C reading). Electronic screening identified 32 people with DLCN ≥5, manual review follow up of electronic records identified 10 people with DLCN ≥5 (diagnostic yield in population 0.86% for electronic searching, 0.27% for manual follow up; nnt= 116 and 371 respectively). In the subset of 360 people with high LDL or TC and statin treatment, who had a manual record search only, 22 people with DLCN ≥5 were identified (diagnostic yield 6.11%, nnt= 16.36). The study was of moderate quality: there was no genetic confirmation of diagnosis and the study was only carried out on active patients who had attended the surgery >3 times in the past 2 years.

In one feasibility study with 35,438 people, based in UK general practices, 831 eligible patients were identified by electronic record screening for total cholesterol >7.5 mmol/L. The GPs

received an educational session, and opportunistic reminders were set up during consultation with the eligible patient or universal postal invitation. People fulfilling possible Simon Broome criteria were invited for GP assessment and referred for specialist diagnosis. 127 (15.3%) people were recruited and completed family history questionnaires. 86 (10.7%) through postal invitation and 41 (4.9%) through opportunistic consultation. The diagnostic yield for possible FH (Simon Broome criteria) was 25.6% (n=32) in primary care, nnt=1,107 in the whole population and 26 for eligible patients). Within 6 months of recruitment, 7 patients had specialist assessment confirming FH (secondary care diagnostic yield of 5.51%, nnt=5,063 and 119): 2 patients with definite FH (28.6%) and 5 patients with possible FH (71.4%). The study was of low quality; there was no genetic confirmation of diagnosis and there was a low uptake rate of the intervention.

Table 3: Summary of included studies: Secondary care pathology databases

Study reference (including study design)	Study population	Method	Outcomes reported	Comments
Bell 2012	84,823	Assessment of FH cases in pathology laboratory database using Simon Broome, Medped and Dutch lipid criteria	Diagnostic yield	Second audit – see Hadfield 2008 in excluded list 84,832 people with 99,467 LDL cholesterol measurements
Bell 2014	196	Pathology laboratory (case control; GP received a phone call from pathologist vs no phone call from pathologist)	Diagnostic yield	
Kirke 2015	4,517	Data from pathology laboratory,	Diagnostic yield	Also recruited from GP practice and workplace; please see primary care section for these outcomes.
Muir 2010	588	Pathology laboratory database; TC value >8.0 mmol/L, lipid stigmata or family history CVD	Diagnostic yield	

Table 4: Lipid clinics or registries

Study reference (including study design)	Study population	Method	Outcomes reported	Comments
Chung 1999	11	Patients with hyperlipidaemia	Diagnostic yield	

Study reference (including study design)	Study population	Method	Outcomes reported	Comments
		attending metabolic clinic Simon Broome criteria used to assess FH		
Clarke 2013	204	Lipid clinic registry. Comparison of diagnostic tools (SB, Dutch criteria) and additional stratification systems to improve identification of FH	Sensitivity and specificity of DLNC and Simon Broome possible criteria to detect FH diagnosed according to definite Simon Broome criteria	Outcomes reported for those with and without tendon xanthoma, with genetic FH
Futema 2013	289	Lipid register. Secondary care	Diagnostic yield	People with definite or possible FH on lipid register
Haralambos 2015	1,206	People with possible FH according to SB or DLCN criteria attending a lipid clinic.	Diagnostic yield	
Heath 2001	227 + 141	People diagnosed with FH according to SB, lipid registry; referred from lipid clinic and GP. Secondary care	Diagnostic yield	227 probands and 141 family members
Hu 2013	314 + 132	Secondary care – lipid clinics	Diagnostic yield	314 first degree relatives and 132 possible index cases
Medeiros 2010/ Bourbon 2007	184 + 418	Lipid registry in Portugal. Secondary care	Diagnostic yield	602 blood samples from 184 index patients and 418 relatives. Adults and children
Taylor 2010	110	Lipid clinic. Secondary care	Diagnostic yield using molecular testing	People referred from adult or paediatric lipid clinics in the UK
Widhalm 2007	263	Lipid clinic, Secondary care	Diagnostic yield using genetic testing	People attending lipid clinic at department of paediatrics, general hospital, university of Vienna.

Table 5: Coronary incident/ CCU

Study reference (including study design)	Study population	Method	Outcomes reported	Comments
Bates 2008	917	Coronary care patients/ CCU.	Diagnostic yield	DLNC used to diagnose FH
De Backer 2015	7,044	CCU	Diagnostic yield	Patients from coronary care centres across Europe
Nanchen 2015	4,778	People with ACS/ CCU setting	Diagnostic yield	Patients hospitalised with Acute coronary syndrome
Pang 2015	175	coronary care unit setting	Diagnostic yield	People with early onset CAD
Wald 2015	231	Young people with MI underwent molecular testing if TC >7 mmol/L. CCU setting	Diagnostic yield, uptake rate	People with MI admitted to hospital, UK

Table 6: Screening (other)

Study reference (including study design)	Study population	Method	Outcomes reported	Comments
Besso 1999	9,673	Neonatal screening in secondary care setting	Diagnostic yield	
Klancar 2015	272	Population screening in Slovenia -children with raised TC and/or family history premature cardiovascular events. Secondary care	Diagnostic yield	
Laurie 2004	65	Population screening in NZ – no further detail. Secondary care	Diagnostic yield	
Wald 2016	10,095	Screening children for FH during immunisations in primary care setting	Diagnostic yield	

2.4 Health economic evidence review (case finding)

2.4.1 Methods

Evidence of cost effectiveness

The Committee is required to make decisions based on the best available evidence of both clinical and cost effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected health benefits.

Evidence on cost effectiveness related to the key clinical issues being addressed in the guideline update was sought. The health economist undertook:

- a systematic review of the published economic literature; and
- new cost-effectiveness analysis.

Economic literature search

A systematic literature search was undertaken to identify health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search in the NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment database (HTA). The search also included Medline and Embase databases using an economic filter. Studies published in languages other than English were not reviewed. The search was conducted on 10 May 2016. The health economic search strategies are detailed in appendix J.

The health economist also sought out relevant studies identified by the surveillance review or Committee members.

Economic literature review

The health economist:

- Identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts. Full papers were then obtained.
- Reviewed full papers against pre-specified inclusion and exclusion criteria to identify relevant studies.
- Critically appraised relevant studies using the economic evaluations checklist as specified in *Developing NICE Guidelines: the manual*.
- Extracted key information about the studies' methods and results into full economic evidence tables (appendix M).
- Generated summaries of the evidence in economic evidence profiles.

Inclusion and Exclusion criteria

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost-utility, cost-effectiveness, cost-benefit and cost-consequence analyses) and comparative costing studies that address the review question in the relevant population were considered potentially includable as economic evidence.

Studies that only reported burden of disease or cost of illness were excluded. Literature reviews, abstracts, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded.

Remaining studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available, then other less relevant studies may not have been included. Where selective exclusions occurred on this basis, this is noted in the excluded economic studies table (appendix L).

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist contained in *Appendix H* of *Developing NICE Guidelines: the manual*.

Economic evidence profile

The economic evidence profile summarises cost-effectiveness estimates. It shows an assessment of the applicability and methodological quality for each economic evaluation, with footnotes indicating the reasons for the assessment. These assessments were made by the health economist using the economic evaluation checklist from *Appendix H* of *Developing NICE Guidelines: the manual*. It also shows the incremental cost, incremental effect and incremental cost-effectiveness ratio for the base case analysis in the evaluation, as well as information about the assessment of uncertainty.

The information contained in the economic evidence profile is explained in Table 7.

Table 7: Explanation of fields used in the economic evidence profile

Item	Description
Study	This field is used to reference the study and provide basic details on the included interventions and country of origin.
Applicability	Applicability refers to the relevance of the study to specific review questions and the NICE reference case. Attributes considered include population, interventions, healthcare system, perspective, health effects and discounting. The applicability of the study is rated as: • Directly applicable – the study meets all applicability criteria or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness. • Partially applicable – the study fails to meet one or more applicability criteria and this could change the conclusions about cost effectiveness. • Not applicable – the study fails to meet one or more of the applicability criteria and this is likely to change the conclusions about cost effectiveness. Such studies would usually be excluded from the review.
Limitations	This field provides an assessment of the methodological quality of the study. Attributes assessed include the relevance of the model's structure to the review question, timeframe, outcomes, costs, parameter sources, incremental analysis, uncertainty analysis and conflicts of interest. The methodological quality of the evaluation is rated as having: • Minor limitations – the study meets all quality criteria or fails to meet one or more quality criteria, but this is unlikely to change the conclusions about cost effectiveness. • Potentially serious limitations – the study fails to meet one or more quality criteria and this could change the conclusions about cost effectiveness • Very serious limitations – the study fails to meet one or more quality criteria and this is highly likely to change the conclusions about cost effectiveness. Such studies would usually be excluded from the review.
Structure and time horizon	This field contains particular issues that should be considered when interpreting the study, such as model structure and timeframe.
Incremental cost effectiveness ratio (ICER)	The incremental cost divided by the incremental effect which results in the cost per quality-adjusted life year gained (or lost). Negative ICERs are not reported as they could represent very different conclusions: either a decrease in cost

Item	Description
	with an increase in health effects; or an increase in cost with a decrease in health effects. For this reason, the word 'dominates' is used to represent an intervention that is associated with decreased costs and increased health effects compared to the comparator, and the word 'dominated' is used to represent an intervention that is associated with an increase in costs and decreased health effects.
Uncertainty	A summary of the extent of uncertainty about the ICER. This can include the results of deterministic or probabilistic sensitivity analysis or stochastic analyses or trial data.

Undertaking new health economic analysis

As well as reviewing the published economic literature for each review question, new economic analysis was undertaken by the health economist.

The following general principles were adhered to in developing the cost-effectiveness analysis:

- Methods were consistent with the NICE reference case.
- The Committee was involved in the design of the model, selection of inputs and interpretation of results.
- Model inputs were based on the systematic review of the clinical literature supplemented with other published data sources where possible.
- When published data were not available, Committee expert opinion was used to populate the model.
- Model inputs and assumptions were reported fully and transparently.
- The results were subject to sensitivity analysis and limitations were discussed.
- The model was quality assured by another health economist within NICE's Centre for Guidelines.

Full methods for the cost-effectiveness analysis conducted for this guideline are described in appendix O.

Cost-effectiveness criteria

NICE's report *Social value judgements: principles for the development of NICE guidance* sets out the principles that GDGs should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- the intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- the intervention cost less than £20,000 per QALY gained compared with the next best strategy.

If the Committee recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'evidence to recommendations' section of the relevant chapter, with reference to issues regarding the plausibility of the estimate or to the factors set out in *Social value judgements: principles for the development of NICE guidance*.

In the absence of economic evidence

When no relevant economic studies were found from the economic literature review, and de novo modelling was not feasible or prioritised, the Committee made a qualitative judgement about cost-effectiveness by considering expected differences in resource use between options and relevant UK NHS unit costs, alongside the results of the clinical review of effectiveness evidence. The UK NHS costs reported in the guideline were those presented to the Committee and they were correct at the time recommendations were drafted; they may have been revised subsequently by the time of publication. However, we have no reason to believe they have been changed substantially.

2.4.2 Results of the economic literature review

A total of 1,012 articles were identified by the search with 990 being excluded based on their title and abstract and 22 full papers ordered. Of these a further 18 articles were excluded. An additional economic evaluation post-dating the search was identified by a member of the committee. Two of the remaining 5 articles related to the same study so 4 studies from 5 articles were included in the economic systematic review. Table 8 contains the economic evidence profile for this review question summarising the results of the studies included in the systematic review, modelling conducted for the previous guideline and the economic model developed for the present update. Full economic evidence tables are contained in appendix M.

The flowchart summarising the number of studies included and excluded at each stage of the review process can be found in appendix K. Appendix L contains a list of excluded studies and the reasons for their exclusion. The following discussion of the 4 included CUAs is summarised in Table 8.

Kerr et al. (2017) investigated the cost effectiveness of genetic cascade testing from index cases with a confirmed monogenic mutation. Advantages of this analysis included using the modern testing pathway specified in the NICE quality standard based on recent developments in genetic testing, long term benefits and cost of treated and untreated FH based on the NICE lipid modification economic model, resource use based on actual FH services in the UK, and the use of HES data to extend the lipid modification model down to age 20. The study found that cascade testing was cost effective with an ICER of £5,806 per QALY. It was only partially applicable to the current decision-making context because it did not include case identification strategies. The study was assessed as having only minor methodological limitations, mainly related to a lack of reporting how the resources (particularly staff) supporting genetic testing were calculated and how gender specific risks were accounted for. There was also no probabilistic sensitivity analysis.

Ademi et al. (2014) compared the cost effectiveness of cascade testing using genetic testing of the relatives of index cases compared with no cascade screening. They also investigated the cost effectiveness of cascade testing based on LDL-C thresholds but scant details are provided on this intervention and it was not included in incremental analysis. The decision tree and Markov model found that cascade testing using genetic testing was cost effective with an incremental cost effectiveness ratio of AUD$3,565 per QALY (2013) (£1,749 (2016)) with a 99% probability of being cost effective. The study was partially applicable to current decision-making purposes. Reasons for downgrading from directly applicable included it being based on the Australian health care system and it did not include interventions relevant to the update such as index case identification through searching databases. It had potentially serious methodological limitations such as a 10 year time horizon, effectiveness of cascade screening was based on a single centre associated with the authors, and inappropriate distributions were used to represent parameter uncertainty in the probabilistic sensitivity analysis.

Chen et al. (2015) investigated the cost effectiveness of genetic cascade screening and lipid cascade screening combined with a statin treatment adherence programme compared with lipid cascade screening alone. It found that genetic cascade screening was extendedly dominated. If the lipid cascade screening and adherence programme intervention was excluded due to irrelevance to the current decision-making context, genetic cascade screening had an incremental cost effectiveness ratio of US$519,813 (£376,138 (2016)) per QALY. At a willingness to pay threshold of US$150,000 per QALY, 99% of the simulated ICERs for lipid screening and adherence strategy vs. lipid screening were cost effective, and 55% of those for genetic screening vs. lipid screening were cost effective. There are two key inputs that limit the generalisability of this study to the NHS. Firstly, the first year screening cost was US$5,528 (£4,000 (2016)) per person and this is likely to far exceed what is incurred by the NHS. In a sensitivity analysis, genetic cascade screening was found to have an ICER below US$150,000 (£108,540 (2016)) per QALY if the first year cost of genetic screening was reduced to US$1,830 (£1,324 (2016)) per person. It is likely that the cost of genetic screening is less than this in the UK. The second parameter that limited generalisability was the dose of 10mg for atorvastatin and treatment effect of 28% reduction in total cholesterol and 38% reduction in LDL cholesterol. A high-intensity statin is recommended to achieve a reduction of 50% from baseline in the original NICE guideline. Inappropriate distributions were used to represent parameter uncertainty in the probabilistic sensitivity analysis. Therefore, the quality assessment of this study found that it was partially applicable with potentially serious methodological limitations.

NCCPC (2008) and Nherera et al (2011) developed an economic model to inform the original guideline on familial hypercholesterolaemia for NICE. Four strategies were compared in the analysis using a decision tree and Markov model framework:

1. Cholesterol method – relatives diagnosed based on elevated LDL-C levels;
2. DNA method – only people with an identified FH-causing mutation were included for cascade testing, with the relatives tested for the family mutation, and secondary cascading for those with the family mutation;
3. DNA+DFH method – As per 2. DNA method, and in addition, in the relatives of definite familial hypercholesterolaemia index cases where no mutation can be found, cascade testing was undertaken using measures of LDL-C levels to identify affected relatives for treatments and for secondary cascading;
4. DNA+DFH+PFH method – as per 2. DNA method, and in addition, cascade testing was undertaken in both definite familial hypercholesterolaemia and probable familial hypercholesterolaemia index cases using LCL-C measures.

The analysis found that the DNA and DNA+DFH strategies were dominated by the cholesterol method. DNA+DFH+PFH had an ICER of £2,676 per QALY in the deterministic analysis and £3,666 per QALY in the probabilistic analysis making it the optimal strategy with 100% probability that it was cost effective using a £20,000 per QALY cost-effectiveness threshold. This study is partially applicable to the decision-making of the current update because it did not include strategies on case identification in primary or secondary care.

2.4.3 Economic modelling

The full report of the economic model developed for this update is provided in appendix O.

Economic modelling was prioritised for the area of case identification and diagnosis for the following reasons:

- New recommendations for systematic case identification in primary care or secondary care were likely to involve a substantial resource impact. This was mainly due to the staff time required in primary care to undertake clinical assessment and refer patients to lipid clinics, and an increased demand for genetic testing.

- The cost effectiveness of new index case identification in primary care and secondary care has not been investigated in any of the studies identified in the economic review.
- The cost of treatment (with atorvastatin) has decreased since the original guideline.
- The cost of genetic testing has decreased since the original guideline.
- The ability to differentiate between monogenic FH and polygenic hypercholesterolaemia due to developments in genetic testing is now an important part of the cascade testing pathway and its relative cost effectiveness.

The following strategies were compared in the analysis:

1. No case identification or cascade testing
2. Genetic cascade testing of the relatives of people with a current clinical diagnosis of definite FH and a functional mutation in the LDLR, APOB or PCSK9 gene
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
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
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
6. Secondary care case identification, clinical assessment using the DLCN criteria, and cascade testing of the relatives of new identified index cases; in addition to cascade testing from currently diagnosed index cases
7. Primary care case identification, secondary care case identification, clinical assessment using the SB criteria, and cascade testing of the relatives of newly identified index cases; in addition to cascade testing from currently diagnosed index cases
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

The diagnostic strategies were simulated via a decision tree, which determined the number of people with treated and untreated monogenic and polygenic hypercholesterolaemia that would enter the long term model and calculated the short term costs of case finding, appointments and genetic testing. The long term model calculated the relevant costs and QALYs for these four types of patients using an augmented version of the model produced for NICE's guideline on Lipid Modification (CG181) in which relevant clinical and cost parameters were updated.

This analysis confirmed that cascade testing is cost-effective and that the addition of primary care case identification strategies is highly cost-effective at an ICER of £1,572/QALY gained. The differences between the DLCN and Simon Broome (possible/probable+definite criteria) in terms of both costs and QALYs were extremely small although the Simon Broome was marginally more cost-effective. Secondary care case identification strategies in people with early MI was not cost effective with ICERs in the region of £70,000/QALY. A large number of parameters were varied in one-way sensitivity analysis with only a few having a material impact on the results. When a much higher (~3.3x the base case) prevalence of FH in the population with early MI was used, the addition of secondary care case identification became cost-effective.Secondary care case ID also became cost-effective in the sensitivity analysis where 12 relatives were assumed to be identified per new index case. Although this estimate has been used in prior analyses, the base case of 2.22 is based on the actual experiences of lipid services in the UK and thought to be a more realistic figure. The results of the model were robust to probabilistic sensitivity analysis with primary care case identification having a 100% probability of being cost effective at a threshold of £20,000/QALY.

A scenario was examined where the stricter “definite only” criteria on the Simon Broome and DLCN were used and although this led to savings through less genetic testing, it also led to lower Net Monetary Benefit values so was considered cost-ineffective.

The de novo analysis is directly applicable to the current decision-making context because it compares a range of case identification strategies with cascade testing alone. The analysis has potentially serious limitations due to the lack of robust data to inform the FH-specific adjustments made to the long term model, which is itself only indirectly relevant to the population under consideration. The results are, however, largely insensitive to even extreme variations in parameters.

Table 8: Economic evidence profile (reverse chronological order)

Study & country	Strategies	Applicability	Limitations	Structure & time horizon	ICER	Uncertainty
NICE 2017	The following strategies were compared in the analysis: 1. No case identification or cascade testing 2. Genetic cascade testing of the relatives of people with a current clinical diagnosis of definite FH and a functional mutation in the LDLR, APOB or PCSK9 gene 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 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 5. Secondary care case identification, clinical assessment using the	Directly applicable	Potentially serious limitations	Decision tree with payoffs taken from lifetime Markov model	Strategy 4 vs Strategy 2: £1,572/QALY Strategy 3 vs Strategy 4: £14,511/QALY Strategy 7 vs Strategy 3: £70,000/QALY All other strategies dominated or extendedly dominated in the base case.	Extensive one-way sensitivity analysis was conducted. Model is only sensitive to somewhat extreme variation in the prevalence of FH in people with early MI and number of relatives approached for cascade testing. There is uncertainty with respect to the most realistic combination of assumptions that should form the base case in long term model, which itself is only indirectly relevant and doesn't include any patients below age 40.

Study & country	Strategies	Applicability	Limitations	Structure & time horizon	ICER	Uncertainty
	Simon Broome criteria, and cascade testing of the relatives of newly identified index cases; in addition to cascade testing from currently diagnosed index cases 6. Secondary care case identification, clinical assessment using the DLCN criteria, and cascade testing of the relatives of new identified index cases; in addition to cascade testing from currently diagnosed index cases 7. Primary care case identification, secondary care case identification, clinical assessment using the SB criteria, and cascade testing of the relatives of newly identified index cases; in addition to cascade testing from currently diagnosed index cases 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					

Study & country	Strategies	Applicability	Limitations	Structure & time horizon	ICER	Uncertainty
	currently diagnosed index cases					
Kerr et al. 2017	• Genetic cascade testing from index cases with confirmed monogenic mutation • Vs. no cascade testing	Partially applicable	Minor limitations	• Decision tree and Markov model	£5,806 per QALY	• Results remain robust for one way sensitivity analysis of level of reduction in LDL-C, number of relatives cascade testing, compliance with lipid modification treatment and cost of Rosuvastatin and ezetimibe • No probabilistic sensitivity analysis
Chen et al. 2015 United States	• Lipid cascade screening • Genetic cascade screening • Lipid cascade screening with an adherence programme to increase compliance with statin treatment	Partially applicable	Potentially serious limitations	• Decision tree and Markov model • Lifetime	• Cascade screening vs. lipid cascade screening: extendedly dominated • Lipid cascade screening with adherence programme vs. lipid cascade screening: US$12,223/QALY (£8,845 (2016))	Using a US$150,000 per QALY threshold (£108,540/QALY) • 99% probability lipid cascade screening with adherence programme is cost effective compared with lipid cascade screening • 55% probability that genetic cascade screening was cost effective compared with lipid cascade screening
Ademi et al. 2014 Australia	• Cascade screening using genetic testing • no cascade screening (cascade screening using LDL-C thresholds was compared to no cascade	Partially applicable	Potentially serious limitations	• Decision tree and Markov model • 10 year time horizon	AUD$3,565/QALY (£1,749.25 (2016))	• 95% confidence interval $2,004 to $5,228 • Cascade screening 99% probability of ICER less than AUD$50,000/QALY (£24,388/QALY)

Study & country	Strategies	Applicability	Limitations	Structure & time horizon	ICER	Uncertainty
	screening in a sensitivity analysis)					
NCCPC 2008 and Nherera et al. 2011 (for NICE CG71) United Kingdom	1.Cholesterol method 2.DNA method 3.DNA+DFH method 4.DNA+DFH+PFH method	Partially applicable	Potentially serious limitations	• Decision tree and Markov model • Lifetime	Vs. cholesterol method: • DNA: dominated • DNA+DFH: dominated • DNA+DFH+PFH: £2,676/QALY	100% probability that DNA+DFH+PFH is cost effective vs. cholesterol method using a £20,000/QALY threshold

Additional details, such as the quality assessment of applicability and methodological limitations, are available in the full economic evidence tables, Appendix M.
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; LDL-C: low density lipoprotein cholesterol; DNA: deoxyribonucleic acid; DFH: definite familial hypercholesterolaemia; PFH: possible familial hypercholesterolaemia

2.5 Evidence statements

2.5.1 Clinical evidence statement

2.5.1.1 Cascade testing - clinical diagnosis

Low to very low quality evidence from:

- 2 studies with 405 people found that direct cascade testing had a range of diagnostic yields for identification of clinically defined FH of 6 to 59%, with a number needed to test of 2 for the Simon Broome criteria and 17 for the Dutch Lipid Network Criteria (DLCN).
- 2 studies with 776 people found that indirect cascade testing had a range of diagnostic yields for identification of clinically defined FH of 30.5 to 37.9%, with a number needed to test of 3 for the Medped criteria and 3 for other non-standardised diagnostic criteria used to diagnose FH.
- 2 studies with 1,879 people found that a combination of indirect and direct cascade testing had a range of diagnostic yields for identification of clinically defined FH of 14.7 to 57.5%, with a number needed to test of 5 for the Simon Broome criteria and 2 for DLCN.

2.5.1.2 Cascade testing - genetic diagnosis

Moderate to very low quality evidence from:

- 5 studies with 7,144 people found that direct cascade testing had a median diagnostic yield for identification of genetically defined FH of 37.5% (range 11.4 to 51.4%), with a number needed to test of 3 (range 2 to 9).
- 1 study with 1,805 people found that indirect cascade testing had a diagnostic yield for identification of genetically defined FH of 44.8%, with a number needed to test of 3.
- 1 study with 642 people found that direct and indirect cascade testing had a diagnostic yield of 55.9%, with a number needed to test of 2.
- 2 studies with 2,910 people found that unknown methods of cascade testing had a diagnostic yield range of 32.8 to 33.9% with a number needed to test of 3.

Cascade testing – uptake rate

Low to very low quality evidence from:

- 3 studies with 1,557 people found a median uptake rate for index individuals for direct cascade testing of FH of 84.1% (range 69.1 to 98.9%).
- 2 studies with 626 people found uptake rates for relatives of index individuals for direct cascade testing of FH ranging from 84.1 to 98.9%.
- 1 study with 2,474 people found an uptake rate for relatives of index individuals for indirect cascade testing of FH of 73.0%.
- 1 study with 2,292 people foumd an uptake rate for relatives of index individuals for both indirect and direct cascade testing of FH of 65.2%.

2.5.1.3 Primary care electronic databases

Very low to moderate quality evidence was found from 6 studies which used distinct methods of case finding within primary care. The studies varied as to whether DLCN or Simon Broome criteria were used, and whether the scores were verified. Four studies with 339,642 people found that searching primary care electronic databases had a median diagnostic yield for identification of FH of 0.178% (range 0.083 to 3.9%), with a number needed to test of 563 (range 116 to 1,250) using the Simon Broome (n=2) or DLCN (n=3) criteria. Five studies with

5,182 people found that electronic search criteria & GP review had a median diagnostic yield for identification of FH of 14.16% (range 1.27 to 29.4%), with a number needed to test of 10 (range 4 to 35) using Simon Broome (n=1) or DLNC (n=5) criteria. From 3 studies with 676 people, genetic testing had a median diagnostic yield for identification of genetically defined FH of 13% (range 0.014% to 37.90%), with a number needed to test of 7 (range 3 to 69).

The most relevant study to UK clinical practice used an informatics tool to identify cases of possible FH (diagnostic yield 0.05%, number needed to test = 2,013), then had targeted case-finding; a nurse assessed people at risk of FH, but not yet screened (overall diagnostic yield 22.2%, number needed to test = 5).

Primary care -uptake rate

Low quality evidence from 1 study with 2,762 people had an uptake rate from primary care searches of index individuals with FH of 26%.

2.5.1.4 Secondary care electronic databases

Pathology databases

Very low quality evidence from:

- 3 studies of 85,616 people found that case finding of FH through pathology databases had a median diagnostic yield for identification of clinically defined FH of 8.5% (range 1.2 to 9.2%), with a number needed to test (DLCN) of 12 (range 11 to 398) and a number needed to test of 27 using Simon Broome criteria.
- 3 studies with 641 people found that case finding of FH through pathology databases had a median diagnostic yield for identification of genetically defined FH of 26.7% (range 12.9 to 30.4%) and a number needed to test of 4 (range 3 to 8).
- 2 studies with 4,517 people had an uptake rate of 13.2% for people at increased CV risk attending clinical assessment, and 61.6% for those at high risk of FH attending specialist review.

Lipid clinics/registries

Very low quality evidence from:

- 4 studies with 1,343 people found that case finding of FH through lipid clinics or registries had a median diagnostic yield for identification of clinically defined FH of 51.0% (range 33.5 to 87.8%), with a number needed to test of 2 for DLCN criteria, and a number needed to test of 2 for both Simon Broome and Medped criteria.
- 6 studies with 1,955 people found that case finding of FH through lipid clinics or registries had a median diagnostic yield for identification of genetically defined FH of 33.3% (range 10.9 to 51.0%), with a number needed to test of 3 (range 2 to 9).

No studies reported uptake rate of testing through lipid clinics or registries.

Coronary units/ MINAP

Moderate to low quality evidence from:

- 4 studies with 12,331 people found that case finding of FH through coronary care units or using the MINAP database had a median diagnostic yield for identification of clinically defined FH of 5.9% (range 1.2 to 14.3%), with a number needed to test of 37 for DLCN and 19 for Simon Broome criteria.
- 1 study with 231 people found that case finding of FH through coronary care units or using the MINAP database had a median diagnostic yield for identification of genetically defined FH of 1.23%, with a number needed to test of 77.

- 1 study with 231 people found that uptake rate for DNA testing in coronary units is 50.1%.

Screening programs

Very low quality evidence from:

- 2 studies with 19,768 people found that case finding of FH through screening programs had a diagnostic yield for identification of clinically defined FH ranging from 0.001 to 0.145%, and a number needed to test ranging from 991 to 1,262.
- 3 studies with 10,432 people found that case finding of FH through screening programs had a median diagnostic yield for identification of genetically defined FH of 17.0% (range 0.4 to 57.0%), and a median number needed to test of 6 (range 2 to 273).
- 1 study with 189 people found that case finding of FH through screening programs had an uptake rate of 43.4%.

2.5.2 Health economic evidence statements

De novo economic modelling conducted for the update found that a strategy of case identification in primary care, clinical assessment using the SB criteria, and cascade testing the relatives of both current and new index cases was the most cost-effective strategy that maximised health benefits at an ICER below the cost-effectiveness threshold compared with seven other strategies, including genetic cascade testing alone. The analysis was assessed as directly applicable with potentially serious limitations.From the published literature, 1 Australian and 2 British studies found that cascade testing was cost effective. One American study found that cascade testing was not cost effective.

2.6 Evidence to recommendations

	Committee discussions
Relative value of different outcomes	The committee identified the critical outcome from the clinical review as the diagnostic yield of people identified with FH through each case finding strategy. The outcome of uptake rate was identified by the committee as an important outcome, as this is a point in the care pathway where a lot of people are lost, and therefore it is crucial to maximise uptake rate.
Quality of evidence	The overall quality of the evidence contributing to the outcomes of interest was very low (ranging from moderate to very low) for cascade testing, low (ranging from moderate to very low) for primary care searching and very low (ranging from moderate to very low quality) for secondary care searching. Generally cascade testing and primary care searching had the greatest diagnostic yield and uptake rate for testing. There was a relatively large volume of evidence. However, the interventions and methods of assessing the diagnosis of FH were heterogeneous. Therefore the committee decided that data on primary care searching should not be combined as the interventions were too heterogeneous. The committee also agreed that the secondary care review should be split into sections for pathology databases, lipid registries or clinics, CCU or MINAP and screening as it was inappropriate to consider these different populations as one section due to the different populations. <u>Cascade testing</u> There was variation in whether direct or indirect cascade testing was used, and in some cases the study did not report which type of cascade testing was used. No studies reported on reverse cascade testing as a single strategy (though Wald 2016 implements reverse cascade testing as part of a screening strategy). Some included studies used methods of diagnosis that are not used in the UK (Medped) and older studies reporting on genetic testing of FH have used methods with lower sensitivity than current methods and are no longer applicable to current practice. A study that assessed child-parent screening (Wald et al 2016), in primary care was

	Committee discussions
	discussed. As this study was based in a primary care setting, and was not cascade screening, it was not included in this section, but in the secondary care screening section. Where evidence for uptake rate was available cascade testing had the highest uptake rate; with direct cascade testing having a greater uptake rate than indirect cascade testing; this is in agreement with the clinical experience of the topic experts. <u>Primary care</u> The overall quality of the evidence was low and included strategies of database searching only and database searching plus nurse assessment. The committee discussed that the most relevant study to UK practice was a study by Green (2016) which used database searching and nurse assessment to identify people with FH. <u>Secondary care</u> The quality of the evidence was very low for pathology databases, lipid clinics/ registries, moderate to low for CCU/ MINAP and very low quality for screening programs. The greatest diagnostic yield and uptake rate was from lipid clinics or registries, where there was a population with early MI; the lowest diagnostic yield was from screening programs. The committee noted that it was difficult to interpret the results from pathology databases, as this may have included data from primary care. The committee also discussed that the NNT depended on the cholesterol level used to identify "at risk" patients.
Trade-off between benefits and harms	The committee considered that the benefit of cascade testing was that affected relatives of an index patient with an identified FH mutation could be identified and treated relatively quickly to reduce the risk of a cardiovascular event. It was noted that direct cascade testing (for genetic and clinical diagnosis) had a greater uptake rate and therefore identified and treated more "at risk" people than indirect cascade testing. For primary care, the committee noted that database searching was an effective method of identifying a lot of people at risk from FH. For secondary care searching, the committee discussed the variation in the population and testing strategies of the different subsections (pathology databases, lipid registries, CCU/MINAP and screening strategies) and that this variation was reflected in the vastly different diagnostic yield and uptake rates of the different sections. Overall, any strategy (cascade testing, primary care or secondary care database searching) was more effective than not undertaking case finding. However, the committee agreed that cascade testing (current practice) and primary care searching were the most comprehensive and practical ways of identifying people who may have FH. The committee did not identify any clinical harms associated with case-finding for FH. The committee discussed the impact of the new evidence on the other recommendations in this section, and decided that they should stand (see recommendations 1.2.2, 1.2.3 and 1.2.4 in the short version of the guideline for these recommendations).
Trade-off between net health benefits and resource use	The committee considered that the weight of published economic evidence, including the economic analysis conducted for the original guideline, found that cascade testing was cost effective. Recent studies are more relevant to current decision-making because of developments in genetic testing and the ability to focus resources on cascade testing from index cases with a confirmed monogenic mutation. A new, unpublished economic analysis was considered by the committee (Kerr et al., 2017). This study compared monogenic cascade testing with no cascade testing and found that cascade testing was cost effective with an ICER of £5,806 per QALY. Having established that cascade testing was cost effective based on existing analyses, including the original guideline, the committee decided that a de novo analysis was required to determine whether case

	Committee discussions
	identification strategies in primary care or secondary care or both in addition to cascade testing were cost effective – evidence that was not available from the published literature. The committee were also interested in the most cost-effective cholesterol threshold for case finding, the relative diagnostic performance between the most popular clinical assessment tools (the Simon Broome criteria and the DLCN criteria), and the optimal threshold in each tool that should be used for referral to a lipid clinic. The prevalence of FH had been estimated within a variety of cholesterol thresholds in the literature but the only threshold for which there was strong evidence (cases were genetically confirmed, within a relevant population and data agreed with known epidemiology) was total cholesterol greater than 9.3 mmol/L. The committee discussed that while this threshold was quite high and would likely miss a large number of cases, it was the only one with strong enough evidence to underpin recommendations with a potentially high resource impact. The results of the analysis confirmed that cascade testing was cost-effective, and showed that the addition of primary care case finding based on a total cholesterol threshold of >9.3mmol/L was cost-effective with an ICER of £1,538/QALY gained. The results were robust to nearly all of the sensitivity analyses but sensitive under some scenarios: higher prevalence of FH in people with early MI (potential new index cases in secondary care), a 'rule in' (definite FH only) profile for the sensitivity and specificity of the clinical assessment tools in primary care, a 'rule in' profile in both primary and secondary care, and multiplying the number of relatives approached for cascade testing four-fold. The committee determined that a 'rule in' profile for clinical assessment tools was likely to miss too many cases of FH due to having a very low level of sensitivity and was associated with lower net monetary benefit values so was not cost effective compared to the less specific but more sensitive criteria. Identifying and contacting 8 relatives per index case was thought to be unlikely to be achieved in clinical practice. The committee discussed that the sensitivities of both clinical assessment tools under the 'rule out' profile (possible or definite FH under the Simon Broome criteria; score >5 under the DLCN criteria) are quite similar and that the associated costs and QALYs were extremely similar. The committee therefore decided to recommend that either tool could be used to decide which patients are referred for genetic testing. While this would theoretically involve a change in current practice as the Simon Broome criteria had previously been recommended in CG71, topic experts advised there is a proportion of primary care clinicians who use the DLCN or do not currently use any clinical assessment tool. The committee discussed that any appropriately-trained clinician working in primary care should be able to recognise the signs and symptoms required to populate the DLCN criteria and noted that improvements to the DLCN are an active area of research so did not want to unduly discourage its use. The model concluded that secondary care case finding in people with an early MI was not cost effective with ICERs in the region of £60-80,000/QALY gained. This was due to the low prevalence of FH in the target population, which would have to triple in order to change the conclusions, which the committee considered unlikely. The committee discussed several limitations of the current analysis, mainly relating to lack of data availability in certain key areas including the true QRISK and age/sex distribution of people likely to be found by the case finding strategies, the relative risks of cardiovascular events in people with and without FH and a total cholesterol above 9.3, the true relative risk of high intensity statin treatment in these people (which was thought to be greater than in the non-FH group) and the proportion of people with and without MI already treated with statins. Despite these limitations, it was noted that the conclusions of the model were robust to even extreme variation in parameters.

	Committee discussions
	The committee discussed the implications of case finding using a blanket total cholesterol threshold of 9.3 for patients of all ages and for patients of both sexes. Particular concern was expressed that patients below the age of 30 have, on average, considerably lower total cholesterol levels than older patients. Therefore, using a single threshold across all age groups would mean that a negligible number of younger patients with FH would be identified through case finding. Furthermore, total cholesterol levels differ by sex across different age groups; for individuals between the ages of approximately 25 to 55, total cholesterol is, on average, higher for males than for females, whereas the reverse is true for individuals outside of this range. Concern was therefore expressed that using a blanket threshold may advantage one sex over another. The de novo economic model developed for this update relied on data from a study which reported a genetically confirmed prevalence of FH above a threshold of 9.3 mmol/L (Futema 2015). These data were not nuanced by age or gender. However, the reported data show that the threshold of 9.3 mmol/L corresponds to the 99.5th percentile of total cholesterol in the study cohort. Therefore, a solution was discussed in which total cholesterol thresholds corresponding to the 99.5th percentile across various age and sex groups could be calculated using alternative, large-sample data from the Health Survey for England (HSE) in order to produce appropriately granular thresholds. Due to the large sample size and wide geographic coverage, the HSE data was seen as a robust source of population level cholesterol values, particularly at the top end of the distribution. In order for the committee to make recommendations nuanced by age or sex groups, the assumption that the proportion of patients with FH in the 99.5th percentile of total cholesterol reported by the Futema study would not be radically lower in each patient subgroup derived from the Health Survey for England data would have to hold. The committee agreed that, since the economic model showed that case finding is highly cost-effective, any reasonable assumptions about these values would not qualitatively change the results. The committee discussed the appropriate number of age categories by which to nuance the case finding threshold. It was felt that splitting the population into a larger number of groups would provide more granularity and ensure that the recommendations addressed variation in cholesterol levels across age groups more accurately. However, the committee also agreed that case finding on a primary care database is a time-consuming activity, and introducing a large number of age groups would substantially increase the workload for GP surgery staff, making the recommendations less likely to be implemented. Furthermore, in the absence of an audit tool for FH case finding, practice staff would have to design and conduct their own searches, which could act as a further barrier to implementation. The committee agreed that specifying thresholds for two age groups (patients aged 16-29 and patients aged >30) struck an appropriate balance between these two competing factors. These groupings appropriately account for the lower total cholesterol levels in younger patients, while retaining a practical number of groups for case finding on a practice system. The committee also discussed the potential for nuancing the threshold by sex. It was noted that if the preferred age groups of 16-29 and >30 were further subdivided by sex, the resulting total cholesterol thresholds would be lower for males than for females across both groups. The committee agreed that such a divide would favour males, as the thresholds do not adequately reflect the period between the ages of 25-55 where, on average, males have a higher total cholesterol than women. It was felt that, to appropriately reflect the intersectionality between age and sex, at least 4 age brackets would be required, resulting in 8 subgroups overall. The committee considered that, on balance, a simpler recommendation with only 2 thresholds based on age would likely result in better guidance uptake and

	Committee discussions
	adherence, and would therefore provide greater benefit to both sexes than a more nuanced recommendation which is impractical to implement. Moreover, the committee noted that the variation in total cholesterol according to patients' age is substantially greater than according to gender, and therefore nuancing recommendations by the former axis is of primary importance. The committee discussed the thresholds for the selected age groups observed in the Health Survey for England data: 7.6 mmol/L for patients aged 16-29 and 9.0 mmol/L for patients aged >30. It was suggested that the threshold for the younger group of patients should be slightly lowered to 7.5 mmol/L in order to be consistent with the threshold for suspecting FH elsewhere in the guideline. The committee agreed that, while this represented a slight departure from the empirical data, it would lend clarity to the guidance, and potentially assist with its uptake. Treating FH is much more cost-effective in younger age groups so it is highly unlikely that slightly lowering the threshold would result in cost-ineffective care. It was also confirmed that the value of 7.5 mmol/L lies within the 95% confidence interval for the 99.5th percentile of total cholesterol for this age group. It was therefore judged that the change is justified by the evidence. The resource impact of reducing the threshold was also discussed, and was estimated to be negligible, given the relatively small number of patients below the age of 30 whose cholesterol levels are recorded. The committee noted that implementing more granular recommendations could be made more practical in the future with an appropriately designed audit tool. Therefore, it was concluded that a research recommendation should be made on this topic. The committee noted that data on the true prevalence of FH within different cholesterol thresholds are sparse and conflicting but that, given the highly cost-effective nature of primary care case finding in populations with total cholesterol above 9.3, it is likely that conducting case finding in lower thresholds would still represent a cost-effective use of NHS resources. The resource impact associated with the various strategies in the model was calculated to be high, however, and any further increases would have to be based on more robust evidence than was available during this update.
Other considerations	Monogenic FH vs polygenic hypercholesterolaemia: genetic testing will identify "true" monogenic FH. Polygenic hypercholesterolaemia presents with the clinical phenotype of FH, which can mimic monogenic FH, however people with polygenic hypercholesterolaemia often have higher triglycerides than people with monogenic FH. The committee discussed that the risk of CHD is lower in people with polygenic hypercholesterolaemia than in people with monogenic FH; no evidence was presented for this, but this was recorded from anecdotal discussion by the committee. Both people with monogenic FH and polygenic hypercholesterolaemia require statin treatment; however, people with polygenic hypercholesterolaemia respond better (need a lower dose of lipid-lowering drugs) because they do not have the LDLR, APOB or PCSK9 defect. The committee discussed that the current gold standard test for FH is genetic testing using next generation sequencing, which captures the three genes of interest: LDLR, APOB and PCSK9. The committee agreed that good quality evidence should have genetic confirmation of FH as a reference standard. The evidence review assessed clinical and genetic cascade testing of FH separately; although there were a small number of studies assessing cascade testing using clinical or genetic methods, the trend was towards a higher diagnostic yield in genetic cascade testing. The committee discussed the issue of dropouts/ non-uptake of testing which is an important issue, and is where a lot of people are "lost" from the care pathway.

	Committee discussions
	It was noted that direct cascade testing can either be via a letter sent by a healthcare professional, or by making contact by phone. It was the committee's opinion that most direct cascade testing in the UK is believed to be via letter, whether direct or indirect (NB. This has equalities issues – ensuring materials are made available in alternative formats, different languages). The setting of cascade testing was also discussed: The committee agreed that cascade testing should be carried out in specialist centres as these settings provide genetic counselling which is necessary when offering people genetic testing (see 2011 genetic counselling guidelines). An issue with GP database searching is the use of Read codes and/or ICD codes: different GP practices and datasets have different codes, for example there is no Read code for tendon xanthoma (a diagnostic criterion for FH). It was also discussed that there may be detection bias arising from the fact that some people listed in primary care databases may have a recorded cholesterol measurement, and these may have different characteristics to those without a cholesterol measurement. There is also inadequate information stored in GPRD that would enable diagnosis to be made using DLCN criteria. The committee discussed that there is an issue with accurate coding of FH; for example, a person with FH, CHD and tendon xanthoma may have a code for FH and CHD, one as a diagnosis and one as a major event and may or may not have a code for tendon xanthoma. The committee noted that, for people 40 years or older. NHS health checks provide a systematic means of measuring and recording cholesterol, and a high uptake of these would enable more people with FH to be identified through primary care case finding. With regards to identification of FH in children of index cases of FH, the committee discussed that diagnosis would now only be made by genetic testing (gold standard), not by obtaining LDL-C concentrations. The original recommendation for identifying FH in children of an affected individual with FH was to use DNA testing if the mutation was known, or LDL-C concentration where a mutation was not identified. Given that adults with a definitive diagnosis of FH will now have an identified mutation, the committee considered that genetic testing of a child (who has a parent with FH) was sufficient to identify FH in the child of a person with FH, and that measuring LDL-C concentration to identify FH in children of affected adults was unnecessary. The committee decided that the recommendation regarding measuring of LDL-C concentration in children to diagnose FH should be stood down to reflect this change in technology and clinical practice. The results for cascade testing support this decision; as genetic identification of FH has a higher diagnostic yield (across direct, indirect and direct and indirect methods) compared to clinical diagnosis; therefore indicating that genetic identification of FH is more effective than clinical methods (e.g. DLCN) alone. The committee discussed and noted that there could be various equalities issues: • Consideration was given to patients where English is not their first language, and there may be the need for translation services. • If either direct or indirect cascade testing is used then written materials should be available in alternative formats/ languages. A translation service would need to be considered if contacting people by phone call. • Families where individuals are estranged, including single parent families and in cases of adoption. • There is regional variation in availability of and access to FH services and genetic testing.

	Committee discussions
	• Ethnicity: in general there is a lack of data on prevalence of FH in different ethnic groups: it has been suggested that FH is less common in people of African family origin. • Gender: males with FH have a risk of MI at an earlier age than females, this reflects the general population. However, in both males and females with FH, there is a greater risk of MI in untreated FH. • Young people: there may be a greater risk of MI in younger people with FH if they remain untreated, Effective early treatment reduces their risk to that of the general population. • Pregnancy/breastfeeding: the treatment for FH is high intensity statin, pregnant or breastfeeding women are not advised to take statins. The committee discussed the need for new research recommendations; there was consensus that more research was needed on the effectiveness of using different LDL-C concentration thresholds in primary care case finding, the effectiveness of secondary care case finding, and the comparative effectiveness of direct and indirect cascade testing. The research recommendations are outlined in more detail in section 2.8

2.7 Recommendations

1. **Suspect familial hypercholesterolaemia (FH) as a possible diagnosis in adults with:**
    - a total cholesterol level greater than 7.5 mmol/l and/or
    - a personal or family history of premature coronary heart disease (an event before 60 years in an index individual or first-degree relative). [2008, amended 2017]

2. **Systematically search primary care records for people:**
    - younger than 30 years, with a total cholesterol concentration greater than 7.5 mmol/l **and**
    - 30 years or older, with a total cholesterol concentration greater than 9.0 mmol/l

    as these are the people who are at highest risk of FH. [2017]

3. **For people with a personal or family history of premature coronary heart disease (an event before 60 years in an index individual or first-degree relative), but whose total cholesterol is unknown, offer to measure their total cholesterol. [2017]**

4. **Carry out cascade testing using DNA testing to identify affected first-and second-and, when possible, third-degree biological relatives of people with a genetic diagnosis of FH. [2017]**

5. **In children aged 0-10 years at risk of FH because of one affected parent, offer a DNA test at the earliest opportunity. If testing of a child at risk has not been undertaken by the age of 10 years, offer an additional opportunity for a DNA test. [2017]**

2.8 Research recommendations

2.8.1 Using different thresholds of low-density lipoprotein cholesterol concentration in primary care case-finding

What is the clinical and cost-effectiveness of using different thresholds of low-density lipoprotein cholesterol (LDL-C) concentration in primary care case- finding?

Why this is important

The clinical community recognises that familial hypercholesterolaemia (FH) is underdiagnosed, with prevalence more likely to be approximately 1 in 250 rather than the widely cited 1 in 500. Searching electronic primary care databases is an effective way of identifying people with FH. One of the ways in which people are identified through electronic primary care database searching is to search using total cholesterol or low-density lipoprotein cholesterol (LDL-C) concentration. Currently, the entire evidence base for identifying cohorts of people with FH through primary care case finding uses a total cholesterol concentration cut-off of 9.3 mmol/l. This is a very high concentration and anecdotal evidence suggests that this identifies older people but may miss younger people with FH. This could lead to missed opportunities to identify and treat people with FH at an earlier age. Research is needed to identify whether using different total cholesterol and LDL-C concentrations to identify people with FH through primary care database searching affects the diagnostic yield of FH. Additionally, there is a lack of data on the ethnicity, age and triglyceride concentration of people with FH identified through primary care database searching. These should be included as outcomes in future research.

Table 9 Specification for research recommendation

PICO	**Population:** People registered with a general practice in England **Intervention:** Searching primary care electronic databases using the following cut-offs: Total cholesterol (TC) concentration: - >7.5 mmol/L LDL-C concentration: - >8.5 mmol/L - 6.5-8.4 mmol/L - 5-6.4 mmol/L - 4-4.9 mmol/L - >4.9 mmol/L **Comparison:** N/A **Outcomes:** Diagnostic yield of people with FH Age of those identified with FH Ethnicity of those identified with FH Triglyceride concentration of people identified with FH
Current evidence base	Currently, the most robust evidence base for identifying cohorts of people with FH through primary care case finding uses a total cholesterol concentration cut-off of 9.3 mmol/L only. More research is

	needed to establish whether there is a greater diagnostic yield when using different LDLC or TC cut-offs. Additionally, there is a paucity of information on the ethnicity, age and triglyceride concentration of people diagnosed with FH, therefore this information should be captured in this question.
Study design	Prospective or retrospective cohort studies

2.8.2 Evaluate the benefits of different search strategies in primary care case finding

What is the clinical and cost-effectiveness of identifying people with FH through primary care case-finding using more factors than low-density lipoprotein cholesterol (LDL-C) concentration alone?

Why this is important

The currently available data only allow for recommendations around primary care case finding for people with FH to be based on LDL-C and age. More sophisticated algorithms incorporating a wider range of potential risks factors (analogous to ones available in other areas, such as the Framingham CVD risk assessment and FRAX osteoporosis score) may allow for more sensitive and specific electronic searches to be conducted, based on data routinely available in primary care systems. This research would also help to address issues around the feasibility and practicality of these searches in primary care.

Table 10: Specification for research recommendation

PICO	**Population:** People registered with a general practice in England **Intervention:** Searching primary care electronic databases using multidimensional algorithms, which may include factors such as: LDL-C concentration Total cholesterol concentration Triglyceride concentration Age Sex Personal history of CVD Family history of CVD **Comparison:** N/A **Outcomes:** Diagnostic yield of people with FH Age of those identified with FH Ethnicity of those identified with FH Triglyceride concentration of people identified with FH
Current evidence base	Currently, the entire evidence base for case finding in secondary care is not robust enough; with the interventions being too disparate to pool and the diagnostic yield being very low. More research is required on the efficacy of case-finding using secondary care databases on particular populations to establish whether it is more clinically and cost-effective to identify FH this was in specific sub-populations (e.g. younger people, smokers v non-smokers).
Study design	Prospective or retrospective cohort studies

2.8.3 Evaluate the benefits of different search strategies in secondary care case finding

What is the clinical and cost-effectiveness of identifying people with FH through secondary care case-finding?

Why this is important

There is a lack of good quality evidence on secondary care case-finding. More research is required to assess the mutation detection rate in people, especially with regards to those that have had MI at different ages, differences in mutation detection between males and females, and in smokers compared to non-smokers. The detection of FH in young people through secondary care searches is of particular importance, as current opinion is that case finding is more likely to identify older people; if more people with FH can be identified at an earlier age, they can benefit from earlier intervention and treatment.

Table 11: Specification for research recommendation

PICO	**Population:** People attending secondary care setting, with data in secondary care databases. **Intervention:** Searching secondary care electronic databases to identify people with clinical FH. **Comparison:** N/A **Outcomes:** Diagnostic yield of people with FH Ethnicity of those identified with FH Triglyceride concentration of people identified with FH Outcomes should be subgrouped by age, gender, age of MI and smoking status.
Current evidence base	Currently, the entire evidence base for case finding in secondary care is not robust enough; with the interventions being too disparate to pool and the diagnostic yield being very low. More research is required on the efficacy of case-finding using secondary care databases on particular populations to establish whether it is more clinically and cost-effective to identify FH this was in specific sub-populations (e.g. younger people, smokers v non-smokers).
Study design	Prospective or retrospective cohort studies

2.8.4 Evaluate the efficacy of direct and indirect cascade testing

What is the clinical and cost-effectiveness of identifying relatives of people with FH through direct cascade testing directly compared to indirect cascade testing?

Why this is important

There is a lack of evidence directly comparing direct cascade testing to indirect cascade testing. More high quality research is required to directly compare the uptake rate amongst relatives of index individuals with FH using direct and indirect cascade testing to establish which is the more effective clinically and with regards to cost.

Table 12: Specification for research recommendation

PICO	**Population:** Relatives of people diagnosed with FH **Intervention:** Direct cascade testing: a healthcare professional makes direct contact with the relatives of the index case already diagnosed with (or identified as having) FH **Comparison:** Indirect cascade (the index case contacts their own relatives themselves) **Outcomes:** Uptake rate of relatives of people with FH contacted via cascade testing Diagnostic yield of FH detected through cascade testing process
Current evidence base	Currently, there are no studies that directly compare direct and indirect cacade testing for identifying relatives of index individuals with FH. Direct comparison of these methods of cascade testing is required to fully inform the clinical and cost-effectiveness of these methods of cascadet testing.
Study design	RCT, Prospective cohort.

3 Evidence review and recommendations: Diagnosis

3.1 Introduction

DNA diagnosis is the gold standard for diagnosing monogenic FH (presence of a mutation in one of the LDR, APOB or PCSK9 genes). Prior to widespread access to DNA testing, a diagnosis of FH could be based on either DNA testing or the Simon Broome criteria. Currently, scoring criteria are more commonly used to assist in identifying people at risk of FH. These scoring criteria attribute a score to personal and family medical history, physical examination, lipid concentrations and genetic mutations; an increasing score reflects an increased likelihood of a diagnosis of FH. In the UK, the two most commonly used scoring criteria are Simon Broome criteria and Dutch Lipid Clinic Network (DLCN) criteria.

DNA testing has changed greatly since the publication of the original guideline in 2008; with Next Generation Sequencing (NGS) now more widely available. This has reduced the cost of DNA testing for FH causing mutations. Given these changes in DNA technology and the use of scoring criteria in the diagnostic pathway, the clinical question has been updated to reflect current clinical practice: whether Simon Broome or DLCN criteria are more effective at identifying people with genetic FH.

3.2 Review question

In adults with suspected FH, what is the clinical and cost effectiveness of different scoring criteria to diagnose FH?

3.3 Clinical evidence review

3.3.1 Methods

This review was conducted according to the process outlined in the review protocol (see Appendix C.2) with the following exceptions:

Where four or more studies were available for all included strata, a bivariate model was fitted using the mada package in R v3.3.1, which accounts for the correlations between sensitivities and specificities. 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 (see Deeks 2010).

Random-effects models (der Simonian and Laird) were fitted for all syntheses, as recommended in the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (Deeks et al. 2010).

Poor sensitivity or specificity was considered as 50% (0.5) or less: moderate sensitivity or specificity was considered >50 and ≤75% and high sensitivity or specificity was considered >75%.

Inconsistency

This criterion applied only when meta-analysis had been performed. I^2 was calculated to assess the heterogeneity of contributing studies. Inconsistency was rated as 'serious' if there was substantial unexplained heterogeneity (I^2>40%) in either of the sensitivity or specificity

analyses, and very serious if there was very substantial heterogeneity (I^2>75%) in either analysis. Visual inspection of the results was used as an additional tool to assess whether there was heterogeneity.

Imprecision:

The GRADE working group recommend downgrading if confidence intervals are wide, but what constitutes 'wide' depends on the specific review. The topic experts were consulted on maximum width of 95% CIs deemed acceptable when considering imprecision around the sensitivity and specificity. A range of >15% in either the sensitivity or specificity estimate was considered serious imprecision and a range of >15% in both sensitivity and specificity was considered very serious imprecision.

A sensitivity analysis was undertaken for the outcomes of DLCN >5, Simon Broome possible and definite and Simon Broome definite; removing data from the Haralambos (2015) study due to reporting of imputed values for the Simon Broome diagnostic accuracy and because this study used a modified DLCN criteria.

It was originally planned that PPV and NPV would be reported where the prevalence of FH was judged to be similar between studies. However, the level of between-study heterogeneity in prevalence was consistently judged to be too great, and therefore PPV and NPV values (specified as a non-critical outcome) were not reported.

3.3.2 Results

A systematic search was conducted (see appendix D) 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 the criteria specified in the review protocol (appendix C.2). Of these, 53 were excluded as they did not meet the criteria and 9 studies met the criteria and were included.

A review flowchart is provided in appendix E.2, and the excluded studies (with reasons for exclusion) are shown in appendix F.2.

Six studies addressed the effectiveness of DLCN criteria to identify genetic FH (Bell 2014; Bell 2014b; Haralambos 2015 Hooper 2012; Kirke 2015; Maglio 2014). Four studies assessed both DLCN and Simon Broome criteria to identify FH compared to genetic methods (Clarke 2013; Futema 2013; Haralambos 2015; Jannes 2015). Bell 2014, Bell 2014b, Kirke 2015 and Maglio 2014 provided information to calculate diagnostic yield only.

Table 13: Summary of included studies

Study reference (including study design)	Study population and setting	Index test	Reference standard (or gold standard)	Accuracy measures
Bell (2014)	196 (100 cases and 96 historical controls) Secondary care – pathology database	DLCN probable or definite	Genetic test for LDLR, APOB and PCSK9 mutations	Diagnostic yield

Study reference (including study design)	Study population and setting	Index test	Reference standard (or gold standard)	Accuracy measures
Bell (2014b)	N=153 (n=30 with DLCN ≥4 underwent genetic testing) Primary care	DLCN ≥4 (probable or definite)	Genetic test for LDLR, APOB and PCSK9 mutations	Diagnostic yield of DLCN to detect genetic FH
Clarke (2013).	N=204 Secondary care – lipid clinic	SB (definite or possible) DLCN definite, probable, possible)	Genetic test – does not state which mutations screened for	Sensitivity and specificity of clinical score to detect genetic FH Diagnostic yield
Futema (2013)	289 probands + another cohort of 220, aged 18 or over. Secondary care – lipid clinic	DLCN (unlikely, possible, probable, definite) or SB (definite, possible, unclassified) scoring criteria	Genetic test for mutations in APOB, PCSK9 or LDLR genes.	Diagnostic yield
Haralambos (2015)	1,206 Secondary care – lipid clinic	SB (definite or possible) modified DLCN definite, probable, possible)	Genetic test for mutations in APOB, PCSK9 or LDLR genes.	Sensitivity and specificity of clinical score to detect genetic FH Diagnostic yield
Hooper (2012)	N=343 (n=337 genetic test where DLCN available) Primary care	DLCN possible, probable or definite	Genetic test for mutations in APOB, PCSK9 or LDLR genes.	Diagnostic yield
Jannes (2015)	N=248 Primary care	DLCN (unlikely, possible, probable, definite), Simon Broome (definite, probable, no)	Genetic test for mutations in APOB, PCSK9 or LDLR genes.	Sensitivity and specificity of DLCN to detect genetic mutation. Diagnostic yield
Kirke (2015)	N=1,316 (n=86 had clinical FH (DLCN>5) Primary and secondary care	DLCN >5 (subset that had genetic testing offered)	Genetic test for mutations in APOB, PCSK9 or LDLR genes.	Diagnostic yield of DLCN to detect genetic FH
Maglio (2014)	N=77 Secondary care – lipid clinic	DLCN >2	Genetic test for mutations in APOB, PCSK9 or LDLR genes.	Diagnostic yield DLCN to detect genetic FH

Table 14: Diagnostic test accuracy results

Study	Sensitivity (95% CI)	Specificity (95%CI)	PPV	NPV	Diagnostic yield (n +ve mutation/ n clinically positive)
Simon Broome: Definite					
Clarke 2013	0.49 (0.40, 0.59)	0.00 (0.00, 0.17)	73.3	55.8	55/75 (73.3%)
Futema 2013	0.48 (0.37, 0.58)	0.91 (0.86, 0.95)	73.3	77.4	44/60 (73.3%)
Haralambos 2015	0.43 (0.38, 0.49)	0.89 (0.87, 0.91)	60.17	80.31	145/241 (60%)
Jannes 2015	0.11 (0.05, 0.20)	1.00 (0.97, 1.00)	100	62.6	8/8 (100%)
Simon Broome: possible + definite					
Clarke 2013	0.88 (0.80, 0.93)	0.16 (0.09, 0.25)	56.0	51.7	98/175 (56%)
Futema 2013	0.89 (0.81, 0.95)	0.33 (0.26, 0.41)	40.6	85.7	82/202 (40.6%)
Haralambos 2015	0.93 (0.89, 0.95)	0.18 (0.15, 0.21)	30.24	86.19	310/1025 (30.2%)
Jannes 2015	0.84 (0.74, 0.92)	0.52 (0.42, 0.61)	53.6	83.1	64/119 (53.8%)
DLCN: Definite (score > 8)					
Clarke 2013	0.56 (0.46, 0.65)	0.81 (0.70, 0.90)	82.2	53.8	60/73 (82.2%)
Futema 20013	0.54 (0.43, 0.65)	0.69 (0.60, 0.77)	53.9	68.7	48/89 (53.9%)
Hooper 2012	0.70 (0.62, 0.78)	0.82 (0.76, 0.87)	70.3	81.8	90/128 (70.3%)
Jannes 2015	0.45 (0.34, 0.56)	0.88 (0.79, 0.94)	77.6	63.5	38/49 (77.6%)
DLCN: probable + definite (score >5)					
Bell 2014	NR	NR	NR	NR	9/29 (31%)
Bell 2014b	NR	NR	NR	NR	4/30 (13.3%)
Clarke 2013	0.76 (0.67, 0.84)	0.57 (0.44, 0.68)	73.2	60.0	82/112 (73.2%)
Futema 2013	0.76 (0.66, 0.85)	0.46 (0.37, 0.55)	48.6	74.1	67/138 (48.6%)
Haralambos 2015	0.98 (0.94, 0.99)	0.22 (0.18, 0.26)	32.76	96.04	171/522 (32.8%)
Hooper 2012	0.91 (0.84, 0.95)	0.52 (0.45, 0.59)	53.7	90.1	116/216 (53.7%)
Jannes 2015	0.77 (0.67, 0.86)	0.56 (0.45, 0.66)	61.9	72.9	65/105 (61.9%)
Kirke 2015	NR	NR	NR	NR	11/86 (12.8%)[a]
DLCN: possible+ probable + definite (score >2)					
Clarke 2013	0.96 (0.91, 0.99)	0.25 (0.17, 0.35)	61.0	85.2	108/177 (61%)
Futema 2013	0.97 (0.90, 0.99)	0.08 (0.04, 0.14)	41.5	76.9	86/207 (41.5%)

Study	Sensitivity (95% CI)	Specificity (95%CI)	PPV	NPV	Diagnostic yield (n +ve mutation/ n clinically positive)
Hooper 2012	1.00 (0.97, 1.00)	0.05 (0.02, 0.09)	39.1	100	128/327 (39.1%)
Jannes 2015	0.96 (0.90 0.99)	0.20 (0.12, 0.29)	52.6	85.7	81/154 (52.6%)
Maglio 2014	NR	NR	NR	NR	50/77 (64.9%)

*(a) *data presented in paper, no original data available*

3.4 Health economic evidence (diagnosis)

3.4.1 Methods

The same methods were used as specified in section 2.4.1.

3.4.2 Results of the economic literature review

A total of 153 papers were identified in the literature search. All were excluded based on title and abstract. No economic studies were included for this review question.

3.4.3 Economic modelling

The evidence gathered for this review question was included in the economic modelling conducted for the case-finding review question. Please see section 2.4.3 and appendix O.

3.5 Evidence statements

3.5.1 Clinical evidence statements

Sensitivity and specificity

Evidence for the accuracy of 2 different diagnostic scoring systems (compared with the gold standard of genetic testing for mutations in LDLR, APOB and PCSK9 genes) was evaluated for different diagnostic thresholds.

Simon Broome criteria

Very low quality evidence from 4 studies with 1,872 people suggested the Simon Broome definite criteria had low sensitivity (0.36 [0.186, 0.581]) and high specificity (0.86 [0.158, 0.995]). Sensitivity analysis (3 studies, 666 people, very low quality evidence) removing the Haralambos (2015) study also showed low sensitivity 0.335 [0.156, 0.578] and high specificity (0.804 [0.073, 0.950]).

Very low quality evidence from 4 studies with 1,872 people suggested the Simon Broome possible and definite criteria had high sensitivity (0.89 [0.845, 0.924] and low specificity (0.287 [0.160, 0.459]). Sensitivity analysis (3 studies, 656 people, very low quality evidence) removing the Haralambos (2015) study also showed high sensitivity 0.87 [0.825, 0.905] and low specificity (0.325 [0.173, 0.526]).

DLCN criteria

Low quality evidence from 4 studies with 1,088 people suggests that DLCN definite criteria (>8) had a moderate sensitivity of 0.567 [0.460, 0.669] and high specificity of (0.802 [0.713, 0.869]).

Low quality evidence from 4 studies with 1,531 people suggested that DLCN probable and definite criteria (>5) had high sensitivity (0.868 [0.711, 0.946]) but had low specificity (0.457 [0.320, 0.601]). Sensitivity analysis (3 studies, 859 people, moderate quality evidence) removing the Haralambos (2015) study showed a high sensitivity of 0.807 [0.716, 0.874] and moderate specificity (0.517 [0.472, 0.561]).

Low quality evidence from 4 studies with 936 people suggested that DLCN possible, probable and definite criteria (>2) had high sensitivity 0.967 [0.939, 0.983] respectively). The specificity was low (0.125 [0.057, 0.253]).

3.5.2 Health economic evidence statements

No economic evidence was identified in the literature for this review question. The DLCN criteria is slightly more expensive to administer than the Simon Broome criteria due to the additional clinical time required to obtain extra information. However, because the DLCN criteria has a higher specificity compared with the Simon Broome criteria, it is likely to result in a reduced use of lipid clinic resources, including genetic testing, through the increased confidence that people who are referred are more likely to have FH.

3.6 Evidence to recommendations

	Committee discussions
Relative value of different outcomes	The committee discussed that sensitivity and specificity were the most important outcomes, and that there needed to be a compromise between high sensitivity (true positive rate) and high specificity (true negative rate). Whilst FH can be treated relatively easily, the committee noted that the test needed to be adequately specific to avoid unnecessary referrals for genetic testing. The committee further discussed that the specificity required depended on whether a one or two stage process was to be used: a two stage process (using a scoring system to decide whether to refer to secondary care for further assessment) would tolerate a lower specificity (higher false positive rate) in the first stage of the process.
Quality of evidence	Very low quality evidence was available for the sensitivity and specificity of the Simon Broome definite criteria and Simon Broome definite + probable criteria to identify people with a genetic mutation. Low quality evidence was available for sensitivity and specificity for the Dutch Lipid Clinic Network (DLCN) criteria (possible, probable, definite, (score >2); DLCN probable and definite criteria, (score >5) and DLCN definite criteria (score >8) to identify people with a genetic mutation. A sensitivity analysis was undertaken for the Simon Broome possible + definite and definite criteria to see whether the removal of the Haralambos (2015) data had any effect. A sensitivity analysis was undertaken for the outcomes of DLCN >5, Simon Broome possible and definite and Simon Broome definite; removing data from the Haralambos (2015) study due to reporting of imputed values for the Simon Broome diagnostic accuracy and because this study used a modified DLCN criteria. There was no significant difference when Haralambos (2015) was removed from the meta-analysis for Simon Broome possible + definite and definite criteria. A sensitivity analysis was also undertaken on DLCN score >5 (probable and definite) as Haralambos (2015) used a modified DLCN criteria, which reduces the score depending on triglyceride concentration. None of the sensitivity analyses made a significant difference to the results.

	Committee discussions
	No evidence was reported for PPV and NPV because the heterogeneity in prevalence rates between-studies was considered to be too large for pooled results to be robust. Results for the outcome of diagnostic yield were reported in section 2: case finding and are not reported here to avoid duplication.
Trade-off between benefits and harms	The committee noted that there is a trade-off between the sensitivity and specificity of diagnostic criteria: the benefit of diagnosis and treatment of FH vs unnecessary referrals of people who turn out not to have FH. The committee discussed that Simon Broome definite criteria had the lowest sensitivity and highest specificity for predicting a positive genetic diagnosis. Consideration was given to the high sensitivity and low specificity of Simon Broome possible + definite criteria: it was discussed that there was very serious inconsistency between studies. The committee went on to assess the evidence for DLCN criteria to predict a genetic FH mutation: The topic experts discussed that the DLCN criteria score of >2 (possible, probable and definite) had excellent sensitivity, but the low specificity could lead to many people who did not need referrals to secondary care receiving them. It was noted that a DLCN score of >5 (probable or definite) gave a high enough sensitivity, however specificity was poor (<50%). Conversely, a DLCN score of >8 (definite) had high specificity but moderate sensitivity, which could lead to a substantial number of people with FH being missed (increased false negatives). The committee concluded that using either a DLCN score of >5 or Simon Broome possible and definite criteria to refer on to genetic testing gave the best compromise between adequate sensitivity and specificity. The Committee agreed that the evidence was not sufficiently robust to be able to determine which of these two alternatives was most appropriate, and therefore agreed it was correct to recommend that either could be used. The committee considered the recommendations in the diagnosis section in terms of this evidence review and decided that recommendations 1.1.4, 1.1.7 to 1.1.12, 1.1.14 and 1.1.16 should stand unchanged.
Trade-off between net health benefits and resource use	This review question was used to inform the economic modelling conducted for case finding. No economic studies were identified in the systematic review. The committee discussed that the DLCN criteria is slightly more expensive to administer than the Simon Broome criteria due to the additional clinical time required to obtain extra information. However, because the DLCN criteria has a higher specificity compared with the Simon Broome criteria, it is likely to result in a more appropriate use of lipid clinic resources, including genetic tests, through the increased confidence that people who are referred are more likely to have FH.
Other considerations	Given that both Simon Broome possible and definite and DLCN criteria >5 are similar with regards to sensitivity and specificity of diagnosing FH, the committee asked the Topic Experts about the feasibility of using either Simon Broome or DLCN criteria in primary care. It was noted that the DLCN criteria could be viewed as being more complex than Simon Broome criteria. The committee discussed that it is currently easier to search primary care records using Simon Broome criteria, due to coding of records. However, in practice, electronic records would only be searched for total cholesterol and/ or LDL-C measurement and the rest of the assessment using either the Simon Broome or DLCN criteria would be undertaken by a healthcare professional. The committee went on to discuss that there may be the need for education amongst health professionals with regards to using DLCN criteria for diagnosing FH in primary care. This is because the DLCN criteria may be less familiar than Simon Broome criteria; however this was not considered an issue because clinicians would now have the option of using either Simon Broome or DLCN criteria to clinically diagnose FH. Furthermore, there is significant overlap in the criteria used by both

	Committee discussions
	Simon Broome and DLCN: both criteria assess LDL-C concentration, presence of DNA mutation, personal and family history and clinical features. It was considered that clinicians who currently assess patients for FH are already familiar with these aspects of FH, and that introducing the option to use DLCN to assess whether a person may have FH was merely a case of becoming more familiar with the DLCN scoring system rather than learning new clinical features or procedures. The committee considered the assessment of children at risk of FH because of one affected parent. It was stated that it is not appropriate to use DLCN or Simon Broome criteria to assess people in this patient group. Children at risk of FH because of an affected parent had previously been assessed using either LDL-C concentration of DNA testing; however the committee discussed this was no longer appropriate and children of people diagnosed with FH should have a DNA test only. The committee discussed the clinical need for further research in this clinical area and added a research recommendation comparing the use of the Simon Broome and DLCN criteria in identifying FH in a general population.

3.7 Recommendations

6. **Use the Simon Broome or Dutch Lipid Clinic Network (DLCN) criteria to make a clinical diagnosis of FH in primary care settings. This should be done by a healthcare professional competent in using the criteria. [2017]**

7. **Refer the person to an FH specialist service for DNA testing if they meet the Simon Broome criteria for possible or definite FH, or they have a DLCN score greater than 5. [2017]**

8. **Inform all people who have an identified mutation diagnostic of FH that they have an unequivocal diagnosis of FH even if their LDL-C concentration does not meet the diagnostic criteria (see recommendation 6). [2008, amended 2017]**

3.8 Research recommendations

3.8.1 Compare the Simon Broome criteria and the DLCN score in a prospective cohort of general population subjects.

What is the clinical and cost-effectiveness of identifying people with FH by using the DLCN score compared to Simon Broome criteria in the general population?

Why this is important

There is a lack of good quality evidence on direct comparison of Simon Broome and DLCN score in diagnosing clinical FH when compared to the gold standard of next generation sequencing for the three common FH-causing genes.

Table 15: Specification for research recommendation

PICO	**Population:** General population **Index test:** Simon Broome criteria

	DLCN score **Reference test:** Next generation sequencing of APOB, PCSK9 and LDLR. **Outcomes:** Sensitivity of mutation detection Specificity of mutation detection Outcomes should be subgrouped by age, gender, age of MI and smoking status.
Current evidence base	Currently, there is no evidence for a direct comparison of Simon Broome and DLCN compared to a reference standard of NGS for all 3 FH causing mutations.
Study design	Cross sectional diagnostic accuracy study

4 Evidence review and recommendations: Management (Statin monotherapy)

4.1 Introduction

Current clinical management of FH routinely includes pharmacological therapy. Statin monotherapy is currently the initial treatment of choice for FH in adults and children. Treatments including bile acid sequestrants, fibrates and nicotinic acid are now infrequently used, as they have been superseded by newer pharmacological treatments such as ezetimibe, alirocumab and evolucumab; therefore a decision was made to only address the efficacy of statin vs placebo, as prescribing practice with regards to older therapies has not changed since the publication of the guideline in 2008. Guidance on ezetimibe, alirocumab and evolucumab has been published by the Technology Appraisals programme, and is not addressed here (although the guideline does now include a cross-reference to these appraisals). An update of this question was required due to a change in costs associated with statin treatment and to identify any further safety information on long term safety of statin therapy in children.

4.2 Review question

What is the clinical and cost effectiveness of statins compared to placebo in improving outcomes in individuals with FH?

4.3 Clinical evidence review

4.3.1 Methods

The methods used to conduct this review are outlined in the review protocol (see Appendix C3).

Imprecision

As stated in the review protocol, the topic experts were asked to provide minimal important differences for the outcomes of this review as there were no published MIDs reported in the literature, No consensus of agreement was reached and therefore default MIDs of 0.75 and 1.25 were used for dichotomous outcomes, and 0.5 x SD of the control group for continuous outcomes.

4.3.2 Results

A systematic search was conducted (see appendix D3) which identified 6,096 articles. The titles and abstracts were screened and 24 articles were identified as potentially relevant. Full-text versions of these articles were ordered and reviewed against the criteria specified in the review protocol (appendix C3). Twenty two studies (including 9 that were included in the original guideline) were excluded from this review as they did not meet the criteria in the review protocol. One Cochrane review (Vuorio 2014) and one RCT (McCrindle 2002) met the inclusion criteria and were included. Four of the studies included in the Cochrane review were excluded from this analysis as their intervention was Lovastatin or Simvastatin, which is not licensed for use in children with heterozygous FH in the UK (Stein 1999; Clauss 2005; de Jongh 2002a; Couture 1988).The excluded studies and the reasons for exclusion are in Appendix F3.

All of the included studies had a population of children and young people; no studies of high intensity statins in adult populations were identified. A summary of the included studies is in Table 18 below and the full data extraction can be found in Appendix G3.

Adults

No studies of high intensity statins compared to placebo in adults with FH were identified. As set out in the protocol, if no RCTs were identified in a direct population then the committee considered it appropriate to extrapolate the effects of high-intensity statins from an indirect population without FH.

CG181 Lipid Modification (published 2014) has a relevant review question on high-intensity statins in a non-FH population:

- What is the clinical and cost-effectiveness of statin therapy for adults without established CVD (primary prevention) and with established CVD (secondary prevention)?

Full details of the review can be found in NICE Clinical Guideline 181, section 11; appendix C (review protocol), appendix G (evidence tables) and appendix I (forest plots).

How is CG181 relevant in terms of the PICO?

The review from CG181 was based on an indirect non-FH population (adults 18 years or over; including those with or without established CVD, Type 1 diabetes, Type 2 diabetes and CKD). The interventions and comparators included in the CG181 review were low, medium and high-intensity statins and placebo. For the purposes of this review, only results for high-intensity statins vs placebo were included; as indicated in the review protocol (Appendix C3). The high-intensity statins include Atorvastatin 20mg, 40mg or 80mg; Rosuvastatin 10mg, 20mg or 40mg and Simvastatin 80mg, Outcomes reported in CG181 were the same as those specified in the FH protocol with the exception of unstable angina and dropouts not being reported in CG181. CG181 reported mean difference in LDL-C concentration at end of follow up; where possible, we used this data to impute the outcomes of % of people seeing a 50% or greater reduction and mean % change in LDL-C.

The committee considered it appropriate to base their discussions of the evidence and recommendations on the evidence from CG181.

How the evidence from CG181 was used

The committee considered the evidence review from CG181 for this review question was relevant as statins have a comparable effect in people with or without FH. However the committee discussed and agreed that they could not just cross refer to the CG181 guidance, as a separate recommendation would be required when considering use of statins in people with FH.

It was decided that the evidence should not be downgraded for indirectness of using a non-FH population for several reasons. A non-FH population is the most appropriate; RCTs of statins v placebo are unethical in a population with FH. Statins are believed to have the same effect on people whether they have FH or not, therefore there is no difference in the action of statins on people with FH compared to people who do not have FH.

CG181 Results

Seven studies were included in the CG181 review for high intensity statins vs placebo. For the outcome of reduction in LDL-C concentration, the pooled results (final concentration mean difference) for high-intensity statin v placebo were 1.26 mmol/L (95%CI 1.23, 1.29). For the individual statins the results are shown in the table 11 below. There was no GRADE or quality assessment for the outcome of reduction in LDL-C concentration.

Table 16: Final LDL-C concentrations for individual high-intensity statins

High intensity statin	Final LDL-C concentration (mmol/L), mean difference (95% CI)
Atorvastatin 20mg	1.70 (1.65, 1.75)
Atorvatatin 80mg	1.30 (1.15, 1.06)[a]
Rosuvastatin 10mg	0.43 (0.12, 0.97)
Simvastatin 80mg	1.35 (1.14, 1.56)

(a) Copied directly from CG181, assumed an incorrect figure

The committee also considered the outcomes of all-cause mortality, CV mortality, non-fatal MI, stroke and adverse events (myalgia, liver adverse events, new-onset diabetes and rhabdomyolysis) reported in CG181. A summary of these results and their quality rating are reported in table 12 below.

Table 17: Outcomes (results and summary of quality) reported in CG181

Outcome	Number of studies	N of patients		Relative effect (95%CI)	Absolute effect	Quality
		Statins	Placebo			
All cause mortality	3	563/14037 (4%)	629/13627 (4.6%)	RR 0.9 (0.8, 1)	5 fewer per 1000 (rom 9 fewer to 0 more)	High
CV mortality	4	186/13283 (1.4%)	254/13292 (1.9%)	RR0.73 (0.61, 0.88)	5 fewer per 1000 (from 2 fewer to 7 fewer)	moderate
Non-fatal MI	4	96/11618 (0.83%)	207/11207 (1.8%)	0.46 (0.37, 0.59)	10 fewer per 1000 (from 8 fewer to 12 fewer)	High
Stroke	4	339/13283 (2.6%)	425/13292 (3.2%)	0.8 (0.7, 0.91)	6 fewer per 1000 (from 3 fewer to 10 fewer)	Moderate
Adverse events						
Myalgia	3	218/3865 (5.6%)	175/3447 (5.1%)	0.95 (0.78, 1.16)	3 fewer per 1000 (from 11 fewer to 8 more)	High
Liver adverse events	4	85/12766 (0.67%)	32/12348 (0.26%)	2.57 (1.71, 3.85)	4 more per 1000 (from 2 more to 7 more)	Moderate
New onset diabetes	1	270/8901 (3%)	216/8901 (2.4%)	1.25 (1.05, 1.49)	6 more per 1000 (from 1 more to12 more)	Moderate
Rhabdomyolysis	4	4/13183 (0.03%)	5/12773 (0.04%)	0.64 (0.2, 2.09)	0 fewer per 1000 (from 0 fewer to 0 more)	Low

(a) This information has been taken directly from CG181; it has not been adapted or changed in any way for the purposes of this guideline.

Table 18: Summary of included studies: children

Study ID	Study population	Intervention & comparator	Outcomes reported
Vuorio 2014 (Cochrane review)	8 RCTs, (4 included in review) with n= 650* children <18 years with FH (diagnosed by genetic testing or clinical criteria)	Pravastatin 5-20mg (Knipscheer 1996), pravastatin 20-40mg (Wiegman 2004), Atorvastatin 10-20mg (McCrindle 2003), rosuvastatin 5-20mg (Avis 2010). All compared to placebo.	Change in LDL-C concentration Myocardial infarction Adverse events: Liver dysfunction Myopathy Rhabdomyolysis Other adverse events Adherence Where an outcome listed in the review protocol is not listed in Cochrane, the original study will be used to extract the data.
McCrindle 2002 (RCT)	N=36 children with FH (diagnosed by a positive family history of hypercholesterolemia or premature atherosclerotic cardiovascular disease in 1st-degree relatives, a minimum fasting LDL-C before enrolment > 4.15 mM/L) and familial combined hyperlipidaemia	Pravastatin 10mg + colestipol v colestipol only	Change in LDL-C concentration Adverse events Compliance

**the original Vuorio publication had n=1,074, however we did not include 4 studies in this review as the intervention was not in the protocol, therefore n=650 of relevant studies.*

A review flowchart is provided in appendix E3, and the excluded studies (with reasons for exclusion) are shown in appendix F3.

4.4 Health economic evidence (statin monotherapy)

4.4.1 Methods

The same methods were used as specified in section 2.4.1.

4.4.2 Results of the economic literature review

A total of 665 papers were identified by the literature search. Three full papers were obtained and reviewed. All full text papers were excluded. No economic studies from the published literature were included in this review question.

4.5 Evidence statements

4.5.1 Clinical evidence statements

Adults

No studies were identified on the use of high-intensity statins in adults with FH. Evidence statements on the effect of high-intensity statins in people without FH can be found in CG181, section 11.7.1, and are reproduced below as they stood at the time of the publication of this update:

High quality evidence showed that high-intensity statins are more effective when compared to placebo at reducing all-cause mortality at up to 5 years, but the effect size is too small to be clinically important [6 studies, n=27,664].

Moderate quality evidence showed that high-intensity statins are more effective when compared to placebo at reducing CV mortality at up to 6 years, but the effect size is too small to be clinically important at up to 5 years, but the effect size is too small to be clinically important [4 studies, n=26,576].

High quality evidence showed that high-intensity statins are more clinically more effective when compared to placebo at reducing non-fatal MI at up to 5 years [4 studies, n=22,825].

Moderate quality evidence suggested that there may be no clinical difference between high-intensity statins when compared to placebo at reducing stroke at up to 5 years, but the direction of the estimate of effect favoured high-intensity statins [4 studies, n=26,575].

High quality evidence showed that there is no clinical difference between high-intensity statins and placebo in causing myalgia at up to 5 years [3 studies, n=7312].

Moderate quality evidence suggested that there may be no clinical difference between placebo and high-intensity statins in causing new-onset diabetes at 2 years, but the direction of the estimate of effect favoured placebo [1 study, n=17,802].

Low quality evidence suggested that high-intensity statin when compared to placebo caused fewer rhabdomyolysis events at up to 5 years, but the direction of the estimate of effect could favour either intervention [4 studies, n=25,965].

Children

Evidence from 3 studies (n=469) indicated that statins were more effective than placebo in reducing serum LDL cholesterol concentration (%) by the end of follow up (up to 1 year). The quality of the evidence was very low.

Evidence indicated that there was no difference between statins and placebo for the following outcomes:

- Number of people experiencing adverse events at 1 month or 6 months (three studies (n=435). Certainty in the evidence ranged from low to very low.
- Number of people with change in aspartate aminotransferase (3 x ULN) at end of follow up. (3 studies (n=470). Certainty in the evidence was low.
- Number of people with change in alanine aminotransferase (3 x ULN) at end of follow up (2 studies (n=398). Certainty in the evidence was low.
- Number of people with Myopathy (change in serum creatinine phosphokinase concentration 10 x ULN). (2 studies (n=227), Certainty in the evidence was low.
- Compliance (%) to rosuvastatin 5mg, 10mg, 20mg or placebo. (1 study, (n=177), certainty in the evidence was low.

The following outcomes: mortality, cardiovascular mortality, non-fatal MI, non-fatal stroke or unstable angina were not reported in any of the included studies.

4.5.2 Health economic evidence statements

No economic studies were identified in the literature for this review question.

4.6 Evidence to recommendations

	Committee discussions
Relative value of different outcomes	Reduction in risk of cardiovascular events, indicated by cardiovascular outcomes (cardiovascular mortality, non-fatal MI, stroke) and reduction in LDL concentration were the most important outcomes.
Quality of evidence	**Adults** For the review of statins vs placebo in the adult population, there was no evidence from a population of adults with FH (it is unethical to carry out placebo controlled trials of statins in people with FH). Therefore the committee decided it was most appropriate to extrapolate the effects of high intensity statins in a non-FH population. The review for the comparison of high intensity statin v placebo in a non-FH population was presented from CG181 Lipid Modification guideline. The evidence and quality assessment from CG181 was presented as it was in the original guideline (no updates or modifications). It was decided that the evidence should not be downgraded for indirectness of using a non-FH population for several reasons: • A non-FH population is the most appropriate • RCTs of statins v placebo is unethical in a population with FH. • Statins have the same effect on people whether they have FH or not, therefore there is no difference in the action of statins on people with FH compared to people who do not have FH. High quality evidence was available for the outcomes of all-cause mortality, non-fatal MI and myalgia. There was moderate quality evidence for the outcomes of cardiovascular mortality, stroke, liver adverse events and new onset diabetes. Low quality evidence was available for the outcome of rhabdomyolysis. Results showed that high-intensity statins have a clinically significant effect in reducing non-fatal MI. There was a trend towards a beneficial effect (but this was not significant) for high-intensity statins in reducing cardiovascular mortality and all -cause mortality. There were more liver related adverse events with high-intensity statins up to 5 years follow up compared with placebo. There was no difference between high-intensity statins and placebo for outcomes of stroke, myalgia, new onset diabetes or rhabdomyolysis. The committee were aware that there are studies on homozygous FH, reporting a reduction of LDL-C with statins and LDL-C apheresis, and shorter term outcome on CHD morbidity. However, people with homozygous FH were excluded from this review. **Children** Five studies were included in the review for statin vs placebo in children. No studies reported the outcomes of mortality, cardiovascular mortality, non-fatal MI, non-fatal stroke or unstable angina. The outcome of percentage reduction in LDLC showed that statins were clinically effective compared to placebo, there was very low quality evidence contributing to this outcome. The outcomes of adverse events, elevated liver enzymes, myopathy and compliance indicated that there was no difference between statins and placebo for these outcomes; all of which had low quality evidence.
Trade-off between benefits and harms	A reduction in LDLC concentration, and resulting reduction in the risk of cardiovascular events must be balanced against the possible adverse events associated with statin use (including elevated liver enzymes and myopathy). The committee noted that there is a lack of evidence on adverse events in long term statin use (i.e. started in childhood and continued for lifetime). **Adults** The committee considered the evidence presented to them on high-intensity statins vs placebo from CG181. The committee unanimously agreed that that high-intensity statins significantly reduced final LDL-C concentration

	Committee discussions
	compared to placebo for pooled high-intensity statins: the committee also agreed that final LDL-C concentration was significantly reduced for individual statins Atorvastatin 20mg and 80mg and Simvastatin 80mg compared to placebo, but not for Rosuvastatin 10mg compared to placebo. The committee noted that whilst the final LDL-C concentration for high-intensity statins was reported in CG181, there was no quality assessment of this evidence and no evidence statements: it was reported in CG181 that this information was included to ensure the information was available for the GDG if they needed to make recommendations about individual drugs and targets. The committee noted that the only outcomes not reported in CG181 that were specified in the protocol for this review were unstable angina and number of dropouts. Whilst this information would have further informed the committee's decision making, they considered that CG181 provided information on the beneficial effect of high-intensity statins on critical outcomes of all-cause mortality, CV mortality, non-fatal MI and stroke, and that they had sufficient information to make recommendations on use of high-intensity statins in people with FH. The committee then went on to discuss the negative effects of high-intensity statins and agreed that there was an increase in liver-related adverse events with high-intensity statins up to 5 years follow-up. The committee concluded that, taking into account the indirect population, high-intensity statins showed benefit which the committee stated they would expect to see in a population with FH. The recommendation on statin therapy in adults was updated from the 2008 guideline; however, it was considered appropriate to maintain the wording about using a statin with the lowest acquisition cost, as no evidence to indicate using a particular statin was considered during this update. The committee considered the effect of the evidence review on the recommendations associated with statin treatment in adults and decided that recommendations 1.3.1.1, 1.3.1.3 and 1.3.1.10 to 1.3.1.16 should stand unchanged. **Children** In children, the use of statins must be balanced against possible developmental adverse events caused by statins; the committee and topic experts discussed that rosuvastatin or pravastatin were most appropriate due to their hydrophilic nature, which makes them less likely to cross the blood-brain barrier. The committee discussed the age at which statin treatment would start; topic experts responded that the age varies, but treatment by the age of 10 was considered appropriate to balance reduction in cardiovascular risk and adverse events. The topic experts discussed that there were no hard outcome measures to assess the efficacy of statins in children (cIMT is hard to monitor and not validated over time), but the general principle was to prescribe the lowest dose that gives a beneficial effect with few adverse effects. The committee considered the effect of the evidence review on the recommendations associated with statin treatment in children and decided that recommendations 1.3.1.17 to 1.3.1.19, and 1.3.1.23 to 1.3.1.27 should stand unchanged.
Trade-off between net health benefits and resource use	There were no included economic studies for this review question. The findings from the clinical review were used to inform the economic modelling conducted for case finding. The committee discussed that rosuvastatin is more expensive than others that are just as effective although it is about to come off patent next year. The committee noted that better diagnosis through case identification and cascade testing will include some children and increase demand for specialist paediatric lipid services. The committee considered that there is no evidence that one statin is safer than another in children.
Other considerations	The committee previously discussed that pregnant or breastfeeding women should not take statins; therefore they should receive appropriate

	Committee discussions
	counselling and advice about cessation of statins prior to pregnancy and whilst breastfeeding. The committee discussed that the previous guideline CG71 had a target of at least 50% reduction in LDL-C concentration with statin treatment. The committee discussed this in the context of the updated evidence presentation and current European guidelines for reduction in LDL-C concentration with statin treatment in people with FH. It was highlighted that an issue is that a person with FH may have a much higher baseline LDL-C concentration than a person without FH; therefore a 50% reduction may not reduce their LDL-C sufficiently. The committee discussed how a target LDL-C may be more appropriate; however there is uncertainty as to what an appropriate target is. Therefore the committee concluded that there was a lack of evidence to change the 50% reduction target and that it was useful to have as a guide as to what reduction in LDL-C concentration was appropriate for treatment with statins. The committee discussed that although simvastatin 80mg is a high-intensity statin, it is unlikely to be used in practice due to a warning issued by the MHRA. With regards to use of statins in children, the committee summarised that that there was a beneficial effect in children and made a recommendation thus “Offer statins to children with FH by the age of 10 years”. The committee discussed that the original recommendation 1.3.1.22 stated “When the decision to initiate lipid-modifying drug therapy has been made in children and young people, statins should be the initial treatment. Healthcare professionals with expertise in FH in children and young people should choose a statin that is licensed for use in the appropriate age group.” The committee agreed that this recommendation was in an outdated style and was too long. The committee were concerned that the new recommendation to prescribe statins did not mention anything about expertise required in prescribers or licensing of the drugs. Therefore the committee agreed that it was appropriate to also make a recommendation on using an appropriately licensed statin for a child with FH, and amend the old recommendation 1.3.1.22 to state that the healthcare professional should have expertise in treating children and young people in a child-focussed setting. The committee discussed and decided that there was a clinical need to make research recommendations on the effect of treatment with long term statins in children, see section 4.8.1. The committee noted the guideline already contained a recommendation that “coronary heart disease risk estimation tools, such as those based on the Framingham algorithm, should not be used because people with FH are already at a high risk of premature coronary heart disease.” The committee agreed this recommendation still remained highly relevant, but that it should be amended to also contain reference to QRISK2 as a tool rthat should not be used in people with FH, as this is now the one commonly used in the UK, and is recommended in other NICE guidelines to use in people who do not have FH.

4.7 Recommendations

9. **Offer a high-intensity statin with the lowest acquistion cost as the initial treatment for all adults with FH and aim for at least a 50% reduction in LDL-C concentration from the baseline measurement. [2017]**

10. **Offer statins to children with FH by the age of 10 years or at the earliest opportunity thereafter. [2017]**

11. **For children and young people with FH, consider a statin that is licensed for use in the appropriate age group. [2017]**

12. **Statin therapy for children and young people should be initiated by a healthcare professional with expertise in treating children and young people with FH, and in a child-focused setting. [2008, amended 2017]**

13. **Coronary heart disease risk estimation tools, such as QRISK2 and those based on the Framingham algorithm, should not be used because people with FH are already at a high risk of premature coronary heart disease. [2008, amended 2017]**

4.8 Research recommendations

4.8.1 Long-term monitoring of sub-clinical atherosclerosis in children with FH who are treated with statin therapy

What are the long-term effects of statin therapy on sub-clinical atherosclerosis in children with FH who are treated with statin therapy?

Why this is important

Although statins are increasing in use, there is still a lack of data on the long-term effects of statins in children. It is particularly important to determine any long-term adverse effects of statin treatment in a population with FH, as people generally take statins for the rest of their lives once treatment starts.

Table 19: Specification for research recommendation

PICO	**Population:** People with FH taking statins **Intervention:** Statin treatment from the age of 10 years, or Statin treatment for >5 years **Comparator:** Statin treatment started after 10 years of age, or Statin treatment for ≤5 years **Outcomes:** Measurements of sub-clinical atherosclerosis cIMT (this was chosen as a commonly used measure in clinical trials of statins, so would allow for comparisons with other data)
Current evidence base	There is no long term data on the effect of statins prescribed in children for a prolonged time. More information is needed on the adverse effects of long term statin therapy.
Study design	Prospective or retrospective cohort studies

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5.1.1 Case finding

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6 Glossary and abbreviations

Please refer to the NICE glossary.

Additional terms used in this document are listed below.

6.1 Glossary

Cascade testing: Cascade testing is a mechanism for identifying people at risk of a genetic condition by a process of family tracing. For FH the test employed is measurement of (LDL) cholesterol in the blood, and/or a DNA test if a disease-causing mutation has been identified in the proband (see below). Cascade testing can be direct or indirect:

Cascade testing, Direct: Direct cascade testing is where a healthcare professional makes direct contact with the relatives of the Index case already diagnosed with (or identified as having) FH

Cascade testing, Indirect; indirect cascade testing is where the Index case contacts their own relatives themselves.

Cascade testing, Reverse: See cascade testing; the difference here is that index case is identified in a paediatric population (e.g. through school population screening or newborn screening), and then the testing cascades up and the parents and older relatives receive cascade testing once an index individual is identified.

Case finding: A strategy of surveying a population to find those who have the specified disease or condition which is under investigation.

Coronary heart disease (CHD): An event is defined as angina, acute coronary syndrome, myocardial infarction, need for coronary artery bypass grafting, need for percutaneous coronary intervention or definite coronary artery disease on coronary angiography.

Dominant pattern of inheritance (autosomal dominant pattern of inheritance): An affected individual has one copy of a mutant gene and one normal gene on a pair of autosomal (i.e. non-sex) chromosomes. Individuals with autosomal dominant diseases have a 50-50 chance of passing the mutant gene, and therefore the disorder, onto each of their children.

Dutch Lipid Network score: A set of criteria used to diagnose FH. The criteria include: family history or clinical history of premature coronary artery disease or peripheral arterial disease, LDL concentration, DNA mutation and physical signs. Each aspect is given a score which leads to the identification of definite, probable, possible or unlikely FH.

First degree relatives: A person's biological parents, brothers and sisters and children.

Heterozygous FH: High LDL cholesterol concentration in the blood caused by an inherited mutation from one parent only. Individuals with FH are at increased risk of premature cardiovascular disease.

High potency statin: Statins can be grouped into low, medium and high intensity according to how much they reduce LDL concentration (expressed as a percentage). A high intensity statin is one which lowers the LDL concentration by more than 40%; and includes atorvastatin at 20, 40 or 80mg; or rosuvastatin at 10, 20 or 40 mg.

Homozygous FH: Very high LDL cholesterol level in the blood caused by an inherited mutation from both parents. Where a person inherits exactly the same affected gene from both parents this is called homozygous FH. When the mutations in the LDL receptor gene (or equivalent) are different, this state is called "compound heterozygous". In general the overall

effect in both states is similar, in that LDL cholesterol concentrations are very high. Both groups of patients have the same clinical pattern and very high risk of cardiovascular disease early in life.

ICER: Incremental cost-effectiveness ratio. This is difference in costs divided by the difference in health benefits.

Index case/ index individual/ proband: The original or "first" patient (proband) in a family who is identified as having FH, and is the starting point for follow up of their family members to identify which other family members have also inherited the causative gene mutation

Monogenic familial hypercholesterolaemia: A mutation in one of the three genes known to cause familial hypercholesterolaemia (LDLR, APOB, or PCSK9)

Mutation: An identified change in the DNA sequence of a gene which is predicted to change the normal function of the gene and so may cause disease.

Polygenic hypercholesterolaemia: inheritance of a greater than average number of common LDL-C-raising alleles, each causing a slight effect, leading to an increase in LDL-C above the diagnostic cutoff.

Premature CHD: For the purpose of this guideline this refers to a coronary event that has occurred below age 60 in an index individual or first-degree relative

QALY: Quality-adjusted life year. This is measure of health benefit that combines both changes in survival and the quality of that survival.

Read code: Read codes are the standard clinical terminology system used in General Practice in the United Kingdom.

Reverse cascade testing: See cascade testing; the difference here is that index case is identified in a paediatric population (e.g. through school population screening or newborn screening), and then the testing cascades up and the parents and older relatives receive cascade testing once an index individual is identified.

Simon Broome register: A computerized research register of individuals with FH, based in Oxford. Research from this voluntary register has led to several publications describing the natural history of FH in the UK. The “Simon Broome Criteria” for diagnosis were based on study of this group of individuals with FH.

Simon Broome criteria: A set of criteria used to diagnose definite or possible FH. The criteria includes clinical history and family history, age-related LDL concentration, clinical signs or identification of a DNA mutation to identify definite FH.

Tendon xanthoma: A clinically detectable nodularity and/or thickening of the tendons caused by infiltration with lipid-laden histiocytes (macrophages in connective tissue). A distinctive feature of FH which most frequently affects the Achilles tendons but can also involve tendons on the back of the hands, elbows, and knees.

6.2 Abbreviations

CAD: Coronary artery disease

CHD: Coronary heart disease

FH: Familial hypercholesterolaemia

HDL: High density lipoprotein

LDL: Low density lipoprotein

TC: Total cholesterol

TG: Triglycerides

Appendices

Appendix A: Standing Committee members and NICE teams

A.1 Core standing members

Name	Role
Steve Pilling (Chair)	Director -NCC Mental Health
Jim Gray	Microbiologist
Jo Josh	Lay member
Grace Marsden	Economist
Julian Treadwell	GP
Parveen Ali	Lecturer (Nurse)

A.2 Condition specific standing members

Name	Role
Simon Corbett	Cardiologist
Sandy Shiralkar	Consultant Vascular & General Surgeon
Tarek Antonios	Senior Lecturer and Consultant Physician
Nazish Khan	Principal Pharmacist Cardiac Services
Jean MacLeod	Consultant Physician in Diabetes and General Medicine

A.3 Topic expert members

Name	Role
Steve Forster	Lay member
Lisa Gritzmacher	Nurse Specialist
Steve Humphries	Emeritus Professor Cardiovascular Genetics
Nadeem Qureshi	Clinical Professor in Primary Care
Uma Ramaswami	Consultant Metabolic Paediatrician

A.4 NICE project team

Name	Role
Anne-Louise Clayton/ Annette Mead	Technical Editor
Ciara Donnelly	Costing lead
Jessica Fielding	PIP Lead
Jenny Kendrick	Information Scientist
Clifford Middleton	Programme Manager
Jamie Elvidge	Health Economist
Rachel O'Mahony	Technical Lead
Joanna Perkin	Digital Editor
Philip Ranson	Communications Lead
Trudie Willingham	Guidelines Coordinator
Sarah Willett	Guideline Lead

Name	Role
Jeremy Wight	Clinical Adviser

A.5 Clinical guidelines update team

Name	Role
Martin Allaby	Clinical Advisor
Emma Banks	Coordinator
Sara Buckner	Lead Technical Analyst
Emma Carter	Administrator
Paul Crosland	Health Economist (up to Feb 2017)
Ross Maconachie	Health Economist (from Feb 2017)
Martin Domanski	Project Manager (from September 2016)
Nicole Elliott	Associate Director (from June 2016)
Hugh McGuire	Technical Advisor
Nitara Prasannan	Support Technical Analyst
Ian Pye	Project Manager (up to September 2016)
Lorraine Taylor	Associate Director (Up to June 2016)

Appendix B: Declarations of interest

The standing committee and topic experts interests have been declared and collated and are available here.

Appendix C: Review protocol

C.1 Case finding

Review Protocol	
Components	**Details**
Review question	What is the clinical-and cost-effectiveness of using the following strategies for identifying people with FH through: • Primary care electronic databases to identify people with a. history of early myocardial infarction (MI) (<60 years) and hypercholesterolemia b. family history of ischemic heart disease and hypercholesterolemia or; • Secondary care electronic databases ○ within cardiac care facilities or cardiac investigation units to identify people with history of early MI (<60 years) and hypercholesterolemia or ○ within pathology departments to identify people through pathology databases with history of early MI (<60 years) and hypercholesterolemia • Direct and Indirect cascade testing (including reverse cascade testing)? The wording of the review question has been changed from the original review question. The original clinical question was "What is the effectiveness (defined as case identification and cost-effectiveness secondarily) of the following strategies for identifying people with FH: • GP note searching using electronic data bases identifying patients with (i) history of early MI (<60 years) and Tcholesterol (TC) >7.5mmol/L (ii) family history of ischemic heart disease and hypercholesterolemia or; • Secondary care registers (i) within coronary care units through identifying patients with history of early MI (<60 years) and Tcholesterol (TC) >7.5mmol/L or (ii) identification of patients through pathology registers with age <60 years and TC>9 mmol/L and LDL>5.5mmol/L or; • Cascade screening The specific changes and reasons for the changes are: 1. To bring the wording into line with current NICE style guidelines, "patients" changed to "people" and "clinical and cost effectiveness" term introduced. 2. To reflect the change in how patient data is stored and searched; the words "GP note searching" was changed to "Primary care electronic database", "records" and "registers" were updated to "databases". The care settings were updated to capture the areas where people with potential FH may receive care; "cardiac care facilities or cardiac investigation units" was added to ensure that all relevant care settings are included in the terms. The specifications of total cholesterol concentrations were replaced by the broader term 'hypercholesterolemia' so that the performance of strategies for identifying FH using different levels of TC or LDL-cholesterol could be assessed, rather than restricting the review to assessing the performance of strategies that use only the TC or LDL-cholesterol concentrations that are used in the Simon Broome or the Dutch Lipid Network criteria for diagnosis of FH .

Background/ objectives	The case identification question was included in CG71 and is being updated to consider new evidence (4 studies) identified during the surveillance process relating to the clinical and cost effectiveness of case identification of FH.
Types of study to be included	Include: Searches for this review will not be restricted by study design. The rationale for this is that filters for observational studies can be unreliable and may not identify all relevant studies indexed in the database. Exclude: For the outcomes of sensitivity and specificity, we will include only those study types that can provide data amenable to use in a 2 x 2 table (case reports and qualitative studies will be excluded). For all other outcomes, any study design with n=>10 will be included. case reports and qualitative studies will be excluded from the review question
Language	English only
Status	All published articles, will be considered for inclusion as this is a new search and therefore will be run with no date limit
Population	▪ People of any age registered with a GP ▪ People < 60 years of age admitted to a cardiac care facility or cardiac investigation unit ▪ People < 60 years of age listed in pathology databases ▪ People of any age identified through direct or indirect cascade testing (including reverse cascade testing) ▪ People < 60 years of age listed in databases with a discharge code of myocardial infarction (MI) or acute coronary syndrome (ACS) ▪ People < 60 years of age listed in the Myocardial Ischaemia National Research Project (MINAP) database
Intervention	Case identification methods For adults • Identification of people through primary care electronic database searches using the following criteria: a. history of early myocardial infarction (MI) (<60 years) and hypercholesterolemia or b. family history of ischemic heart disease and hypercholesterolemia • Identification of people through cardiac care facility or cardiac investigation databases using the following criteria: a. history of early MI (<60 years) and hypercholesterolemia • Identification of people through pathology databases • Identification of people < 60 years of age listed in the Myocardial Ischaemia National Research Project (MINAP) database For both adults and children • Direct and indirect cascade testing • Reverse cascade testing
Comparator	• All interventions listed above will be compared to no formal case finding (including incidental case finding) • Indirect and direct cascade testing in children and adults will also be compared to each other (indirect testing will be compared to direct testing in adults;

	indirect testing will be compared to direct testing in children; cascade testing in adults will not be compared to cascade testing in children)
Outcomes	For all testing strategies: • Sensitivity for detection of people with FH • Specificity for detection of people with FH • Number of individuals identified in proportion to those assessed (diagnostic yield) • Uptake rate of testing For the comparisons of indirect and direct cascade testing and reverse cascade testing only: • Proportion of people referred for treatment
Any other information or criteria for inclusion/exclusion	The committee will be sent the list of included and excluded studies prior to the committee meeting. The committee will be requested to cross check whether any studies have been excluded inappropriately, and whether there are any relevant studies they know of which haven't been picked up by the searches.
Analysis of subgroups or subsets	No population subgroups were identified where identification of FH may require further considerations in addition to those for the general population. For cascade testing we will subgroup by children and adults
Data extraction and quality assessment	Sifting • Full double sifting will not be conducted due to the anticipated large number of studies returned when a new search is completed without date limits. The support analyst will sift 10% of the database to assess agreement of included studies. If there is disagreement for this 10% sample, a further 10% will be double sifted by the support analyst to quality assure study inclusion. (In cases of further uncertainty, the lead technical analyst will discuss with the technical adviser Data extraction: • Information from included studies will be extracted into standardised evidence tables. Extracted data will be checked by the support analyst. Critical appraisal: The following checklist will be used to assess the quality of each included study 1. Joanna Briggs checklist for case series studies (http://joannabriggs.org/assets/docs/sumari/ReviewersManual-2014.pdf)checkilst will be used. 2. For other study types (Diagnostic test accuracy studies, RCTs, observational studies), the corresponding NICE checklists will be used. Quality assessment: • GRADE methodology will be used to assess the quality of evidence for each outcome as follows; ○ Risk of bias will be assessed using the critical appraisal checklist. The quality of the outcomes will not be downgraded if the population of the study does not have FH diagnosed by DNA analysis. Diagnosis of FH should be by either Simon Broome criteria or the Dutch Lipid Network criteria. ○ Inconsistency will be assessed using the I^2 value where we can pool data. ○ Indirectness will be assessed using population, intervention, comparison and outcomes for comparative studies. For all other study

	types indirectness will be assessed using population, intervention and outcomes. ○ Imprecision will be assessed by analysing the surrogate outcome of number needed to test: as this question addresses the issue of screening in a population, we need to know the number needed to test in order to identify 1 extra case and thus compare the effectiveness of the different strategies. For the outcome of diagnostic yield, we will assess imprecision using the range around the point estimate, an MID of 1 will be used. For the outcomes of sensitivity and specificity, it is envisaged that the default thresholds of 95% will be used to assess imprecision, this will be discussed with the committee. Imprecision will not be assessed for uptake rate because we do not anticipate there being an MID based on the quality standard for FH (QS41). For the outcome of people referred to treatment, the topic experts will be asked to provide MIDs. Reliability of quality assessment: • The following quality assurance mechanisms will be in place: ○ Internal QA by support analyst and CGUT technical adviser on the quality assessment that is being conducted. ○ The committee will be sent the evidence synthesis prior to the committee meeting; they will be asked to comment on the quality assessment, which will serve as a further QA function.
Strategy for data synthesis	Due to the nature of the review and the outcomes reported, it is anticipated that meta-analysis will not be undertaken. The results will be reported in a modified GRADE table. COMET and published literature will be checked for appropriate minimal important differences (MID) for each outcome and if none are available topic experts will be asked to provide MID's. Analyses and results will be presented in modified GRADE profiles and summary evidence statement formats.
Searches	• **Sources to be searched** ○ Clinical searches -Medline, Medline in Process, Embase, Cochrane CDSR, CENTRAL, DARE (legacy records), HTA and PubMed. ○ Economic searches -Medline, Medline in Process, Embase, PubMed, NHS EED (legacy records) and HTA, with economic evaluations and quality of life filters applied. • **Supplementary search techniques** ○ None identified • **Limits** ○ Studies reported in English ○ Study design – no study filter will be applied ○ Animal studies will be excluded from the search results ○ Conference abstracts will be excluded from the search results in Embase ○ No date limit will be applied
Key papers	**Papers identified through surveillance process:** **Economics:** Ademi Z, Watts GF, Juniper A et al. (10-9-2013) A systematic review of economic evaluations of the detection and treatment of familial hypercholesterolemia. [Review]. International Journal of Cardiology 167:2391-2396.

	Pears R, Griffin M, and Watson M. (2014) The reduced cost of providing a nationally recognised service for Familial hypercholesterolaemia. Open Heart 1:e000015. Ademi Z, Watts GF, Juniper A et al. (10-9-2013) A systematic review of economic evaluations of the detection and treatment of familial hypercholesterolemia. [Review]. International Journal of Cardiology 167:2391-2396. Benn M, Watts GF, Tybjaerg-Hansen A et al. (2012) Familial hypercholesterolemia in the danish general population: prevalence, coronary artery disease, and cholesterol-lowering medication. Journal of Clinical Endocrinology & Metabolism 97:3956-3964. (Erratum in J Clin Endocrinol Metab. 2014 Dec;99(12):4758-9.) **Cascade screening:** Talmud PJ, Shah S, Whittal R et al. (2013) Use of low-density lipoprotein cholesterol gene score to distinguish patients with polygenic and monogenic familial hypercholesterolaemia: a case-control study. Lancet 381:1293-1301. Wald DS, Kasturiratne A, Godoy A et al. (2011) Child-parent screening for familial hypercholesterolemia. Journal of Pediatrics 159:865-867. **Screening:** Besseling J, Kindt I, Hof M et al. (2014) Severe heterozygous familial hypercholesterolemia and risk for cardiovascular disease: a study of a cohort of 14,000 mutation carriers. Atherosclerosis 233:219-223. **Primary care:** Weng SF, Kai J, Andrew Neil H et al. (2015) Improving identification of familial hypercholesterolaemia in primary care: derivation and validation of the familial hypercholesterolaemia case ascertainment tool (FAMCAT). Atherosclerosis 238:336-343. <u>Studies in progress:</u> • Two large studies on the utility of carrying out FH case finding in general practice will be published shortly [no further details provided]. • A study funded by the MRC on Child-parent Cascade Testing is likely to report in 2016 [no details provided]. • A Health Technology Assessment has been proposed to examine total cholesterol cut-offs for FH using The Health Survey for England Time Series Dataset and the QRESEARCH large consolidated database [no further details provided]. • BHF funded work being carried out to look at the improvement in cost effectiveness of cascade testing only in those with a monogenic cause and how reduction in costs of off patent statins influences QALYS and ICER. To report 2016.

C.2 Diagnosis

Review Protocol	
Components	**Details**
Review question	In adults with suspected FH, what is the clinical and cost effectiveness of different scoring criteria to diagnose FH?

	The wording of the review question has been changed from the original review question. The original clinical question was: • In adults and children, what is the effectiveness of the following tests to diagnose familial hypercholesterolaemia (FH): o Biochemical assays? o Clinical signs and symptoms? o DNA testing? o Combinations and/or sequences of above? What is the effectiveness of DNA testing in all people (adults and children) who are suspected to have FH? What is the effectiveness of DNA testing for FH mutations among relatives of people with identified mutations for FH?
Background/ objectives	This question was identified as requiring updating during the 6 year surveillance process. Changes in DNA testing technology, and costs associated with diagnosis and management of FH were the main drivers of the update.
Population	Adults with suspected FH
Index tests	<u>In adults:</u> • Scoring criteria, to include: o Definite FH according to the Simon Broome criteria o Possible or definite FH according to the Simon Broome criteria o Definite FH according to the DLCN criteria (>8) o Probable or definite FH according to the DLCN criteria (>=6) o Possible, probable or definite FH according to the DLCN criteria (>=3)
Reference test	<u>Adults:</u> • DNA testing (For any mutation in all 3 FH-causing genes [LDLR, APOB and PCSK9]).
Outcomes	<u>Adults:</u> Sensitivity Specificity Positive predictive value (PPV) Negative predictive value (NPV) Diagnostic yield (number of people who have SB or DLCN scoring who progress to a positive diagnosis with genetic testing)
Type of review question	<u>Adults:</u> Diagnostic test accuracy (DTA)
Types of study to be included	Adults: DTA review: Cross-sectional studies
Language	English language
Status	Published papers, after 2008. Papers included in the original guideline will be considered for inclusion.

Any other information or criteria for inclusion/exclusion	The committee will be sent the list of included and excluded studies prior to the committee meeting. The committee will be requested to check whether any studies have been excluded inappropriately, and whether there are any relevant studies they know of which haven't been picked up by the searches or have been incorrectly sifted out.
Analysis of subgroups or subsets	Adults with: 1. Definite FH according to the Simon Broome criteria 2. Possible or definite FH according to the Simon Broome criteria 3. Definite FH according to the DLCN criteria (>8) 4. Probable or definite FH according to the DLCN criteria (>=6) 5. Possible, probable or definite FH according to the DLCN criteria (>=3)
Data extraction and quality assessment	<u>Sifting</u> Relevant studies will be identified through sifting the abstracts and excluding studies clearly not relevant to the PICO. In the case of relevant or potentially relevant studies, the full paper will be ordered and reviewed, whereupon studies considered not to be relevant to the topic will be excluded. *i) Selection based on titles and abstracts* A full double-sift of titles and abstracts will not be conducted due to the nature of the review question (typical diagnostic test accuracy review); a support analyst will sift a 10% sample of titles and abstracts, and % agreement will be assessed. Where the percentage is less than 100%: - Any papers identified by the support analyst that were not identified by the lead analyst, the full text will be ordered and assessed for inclusion - If agreement is less than 95%, a further 10% sample will be sifted by the support analyst to ensure rigorous identification and selection of studies. *ii) Selection based on full papers* A full double-selecting of full papers for inclusion/exclusion will not be conducted due to the nature of the review question (as mentioned above). However in cases of uncertainty the following mechanisms will be in place: - technical analyst will discuss with a support technical analyst - comparison with included studies of other systematic reviews - recourse to members of the committee <u>Data extraction</u> Information from included studies will be extracted into standardised evidence tables. <u>Critical appraisal</u> The risk of bias of each included study will be assessed using standardised checklists available in the NICE manual for diagnostic studies identified: o QUADAS 2 <u>Quality assessment</u> GRADE methodology will be used to assess the quality of evidence on an outcome basis: o Risk of bias will be assessed using critical appraisal checklists (QUADAS2) o Inconsistency will be assessed using I^2:

	▪ 0-40%: no serious ▪ 41-70%: serious ▪ 71-100%: very serious o Indirectness will be assessed after considering the population, index and reference test and outcomes of included studies, relative to the target population; o Imprecision: For the outcomes of sensitivity and specificity, imprecision will be assessed using the default thresholds of 95%; *please note, a post-hoc change to the review protocol was made with respect to assessing inconsistency and imprecision. We did not originally specificy the software that would be used to undertake meta-analysis; it was decided that the meta-analysis would be undertaken in R to provide a summary statistic and therefore the results reported were sensitivity and false positive rate (not specificity). Inconsistency and imprecision were therefore based on sensitivity and false positive rate. *Reliability of quality assessment:* A full double-scoring quality assessment will not be conducted due to the nature of the review question (typical diagnostic accuracy review) and the studies that are likely to be included. Other quality assurance mechanisms will be in place as the following: • Internal QA (10%) by CGUT technical adviser on the risk of bias and quality assessment that is being conducted. Any disagreement will be resolved through discussion. The committee will be sent the evidence synthesis prior to the committee meeting and the committee will be requested to comment on the quality assessment, which will serve as another QA function.
Strategy for data synthesis	If possible, where there are 2 or more studies, a meta-analysis of available study data will be carried out to provide a more complete picture of the evidence body as a whole. A random effects model will be used as it is indicated that there is variation in test accuracy between included studies, which is too big to be explained by chance. A random effects model provides an average accuracy of each test and describes the variability of the test. If only a single study is available for each parameter then the relevant outcomes from this study will be reported in an appropriate form. Where four or more studies were available for a particular analysis, a bivariate model was fitted using the mada package in R v3.3.1, which accounts for the correlations between sensitivities and specificities. Where sufficient data were not available, separate pooling was performed for sensitivity and specificity, using Microsoft Excel. This approach is likely to somewhat underestimate test accuracy (see Deeks 2001). Random-effects models (der Simonian and Laird) were fitted for all syntheses, as recommended in the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (Deeks et al. 2010). A narrative evidence summary outlining key issues such as volume, applicability and quality of evidence and presenting the key findings from the evidence as it relates to the topic of interest will be produced
Searches	• Sources to be searched: o Clinical searches -Medline, Medline in Process, PubMed, Embase, Cochrane CDSR, CENTRAL, DARE (legacy records) and HTA. o Economic searches -Medline, Medline in Process, PubMed, Embase, NHS EED (legacy records) and HTA, with economic evaluations and quality of life filters applied.

	• Supplementary search techniques
	  ○ If relevant systematic reviews are identified, the reference list will be analysed for any further studies relevant to the question.
	• Limits
	  ○ Studies reported in English
	  ○ Animal studies will be excluded from the search results
	  ○ Conference abstracts will be excluded from the search results
	  ○ The search will be run from 2008 to the present

Key papers	*No key papers identified by topic experts.* 1. Oosterveer DM, Versmissen J, Yazdanpanah M et al. (2009) Differences in characteristics and risk of cardiovascular disease in familial hypercholesterolemia patients with and without tendon xanthomas: a systematic review and meta-analysis. Atherosclerosis 207:311-317. 2. Sharma P, Boyers D, Boachie C et al. (2012) Elucigene FH20 and LIPOchip for the diagnosis of familial hypercholesterolaemia: a systematic review and economic evaluation. [Review]. Health Technology Assessment (Winchester, England) 16:1-266. 3. Norsworthy PJ, Vandrovcova J, Thomas ER et al. (2014) Targeted genetic testing for familial hypercholesterolaemia using next generation sequencing: a population-based study. BMC Medical Genetics 15. 4. Hinchcliffe M, Le H, Fimmel A et al. (2014) Diagnostic validation of a familial hypercholesterolaemia cohort provides a model for using targeted next generation DNA sequencing in the clinical setting. Pathology 43:60-68. 5. Vandrovcova J, Thomas ER, Atanur SS et al. (2013) The use of next-generation sequencing in clinical diagnosis of familial hypercholesterolemia. Genetics in Medicine 15:948-957. 6. Futema M, Plagnol V, Whittall RA et al. (2012) Use of targeted exome sequencing as a diagnostic tool for Familial Hypercholesterolaemia. Journal of Medical Genetics 49:644-649. 7. Pears R, Griffin M, and Watson M. (2014) The reduced cost of providing a nationally recognised service for Familial hypercholesterolaemia. Open Heart 1:e000015.

C.3 Management (statin monotherapy)

Review Protocol	
Components	**Details**
Review question	What is the clinical and cost effectiveness in improving outcome in individuals with FH of the following monotherapy: • Statins versus placebo? The wording of the review question has been changed from the original review question. The original clinical question was: • What is the effectiveness in improving outcomes in individuals with FH of the following monotherapies: ○ Statins versus placebo

	○ Resins (bile acid sequestrants) versus placebo ○ Niacin versus placebo ○ Fibrates versus placebo ○ Fish oils (omega 3 fatty oils) versus placebo ○ Ezetimibe versus placebo)?
Background/ objectives	This area was identified as requiring updating during the 6 year surveillance process. New evidence was highlighted that was relevant to statin treatment in adults and children with FH; this area is being updated here. With regards to statin treatment in adults with FH, the surveillance process identified that new studies on statins in adults may have an impact on the effectiveness data for the Health Economics model.
Population	Adults and children with heterozygous FH
Intervention	In adults, high intensity statins: • Atorvastatin 20mg,40mg or 80mg • Rosuvastatin 10, 20 or 40mg • Simvastatin 80mg In children, the following at any dose: • Atorvastatin • Rosuvastatin • Pravastatin
Comparator	Placebo
Outcomes	All-cause mortality Cardiovascular events: • Cardiovascular mortality • Non-fatal MI • Nonfatal stroke • Unstable angina LDL-C concentration: • % of people seeing a 50% or greater reduction • mean % change on LDL-C Number of people with adverse effects Adherence: • Number of drop outs due to lack of efficacy • Number of drop outs due to lack of tolerance • Number of people switching to alternative treatment
Type of review question	Intervention
Types of study to be included	For the population of adults and children with FH, only RCTs will be included. If no evidence is identified on the direct population of people with FH, then we will refer to indirect evidence with a population of people with hypercholesterolaemia. A recent systematic review on the effect of statin v placebo in people with hypercholesterolaemia was undertaken for CG181 Lipid

	Modification guideline (2014), and the committee agreed that this data can be used to extrapolate to the FH population. Abstracts, posters, reviews, letter/editorials, foreign language publications and unpublished studies will be excluded.
Language	English language only.
Status	Published studies (full text only) from 2008 onwards. Studies included in the relevant comparison in the original guideline will also be considered.
Any other information or criteria for inclusion/exclusion	The committee will be sent the list of included and excluded studies prior to the committee meeting. The committee will be requested to check whether any studies have been excluded inappropriately, and whether there are any relevant studies they know of which haven't been picked up by the searches or have been incorrectly sifted out. Evidence on Ezetimibe is not included in this review as a TA (TA385) was recently published (February 2016) and incorporated into CG71. Evidence on Alirocumab (TA393) and Evolocumab (TA394) is also not included in this review as Technology Appraisals were published in June 2016.
Analysis of subgroups or subsets	Adults with FH Children with FH
Data extraction and quality assessment	<u>Sifting</u> Relevant studies will be identified through sifting the abstracts and excluding studies clearly not relevant to the PICO. In the case of relevant or potentially relevant studies, the full paper will be ordered and reviewed, whereupon studies considered not to be relevant to the topic will be excluded. *i) Selection based on titles and abstracts* A full double-sift of titles and abstracts will not be conducted due to the nature of the review question (typical intervention question); a support analyst will sift a 10% sample of titles and abstracts, and % agreement will be assessed. Where the percentage is less than 100%:; - Any papers identified by the support analyst that were not identified by the lead analyst, the full text will be ordered and assessed for inclusion - If agreement is less than 95%, a further 10% sample will be sifted by the support analyst to ensure rigorous identification and selection of studies. *ii) Selection based on full papers* A full double-selecting of full papers for inclusion/exclusion will not be conducted due to the nature of the review question (as mentioned above). However in cases of uncertainty the following mechanisms will be in place: - technical analyst will discuss with a support technical analyst - comparison with included studies of other systematic reviews - recourse to members of the committee <u>Data extraction</u> Information from included studies will be extracted into standardised evidence tables. <u>Critical appraisal</u>

	The risk of bias of each included study will be assessed using standardised checklists available in the NICE manual for intervention/observational studies identified: ○ NICE RCT checklist <u>Quality assessment</u> GRADE methodology will be used to assess the quality of evidence on an outcome basis: ○ Risk of bias will be assessed using critical appraisal checklists ○ Inconsistency will be assessed using I^2: ▪ 0-40%: no serious ▪ 41-70%: serious ▪ 71-100: very serious ○ Indirectness will be assessed after considering the population, intervention and outcomes of included studies, relative to the target population; ○ Imprecision will be assessed using whether the confidence intervals around point estimates cross the MIDs for each outcome. COMET and published literature will be checked for appropriate minimal important differences (MID) for each outcome and if none are available Topic Experts will be asked to provide MID's. • Where evidence from CG181 is referred to we will undertake GRADE assessment of the evidence as it applies to the FH population. *Reliability of quality assessment:* A full double-scoring quality assessment will not be conducted due to the nature of the review question (typical intervention review) and the studies that are likely to be included. Other quality assurance mechanisms will be in place as the following: • Internal QA (10%) by CGUT technical adviser on the risk of bias and quality assessment that is being conducted. Any disagreement will be resolved through discussion. The committee will be sent the evidence synthesis prior to the committee meeting and the committee will be requested to comment on the quality assessment, which will serve as another QA function.
Strategy for data synthesis	• If possible a meta-analysis of available study data will be carried out to provide a more complete picture of the evidence body as a whole. A fixed effects model will be used as it is expected that the studies will be homogenous in terms of population and we can assume a similar effect size across studies. A random effects model will be used if this assumption is not correct. A narrative evidence summary outlining key issues such as volume, applicability and quality of evidence and presenting the key findings from the evidence as it relates to the topic of interest will be produced Where evidence from CG181 is referred to, the original meta-analysis will be used in committee decision making, where appropriate to an FH population. In the scenario where the studies in the original review have specific subgroup data that applies to people with FH, this data will be extracted and used for the basis of decision making.
Searches	• Sources to be searched: ○ Clinical searches -Medline, Medline in Process, PubMed, Embase, Cochrane CDSR, CENTRAL, DARE (legacy records) and HTA.

	○ Economic searches -Medline, Medline in Process, PubMed, Embase, NHS EED (legacy records) and HTA, with economic evaluations and quality of life filters applied. • Supplementary search techniques ○ If relevant systematic reviews are identified, the reference list will be analysed for any further studies relevant to the question. • Limits ○ Studies reported in English ○ Study design SR and RCT filters will be applied, observational studies filter wil be applied for the long-term adverse events question, ○ Animal studies will be excluded from the search results ○ Conference abstracts will be excluded from the search results ○ The search will be run from 2008 to the present
Key papers	1. Ara R, Tumur I, Pandor A et al. (2008) Ezetimibe for the treatment of hypercholesterolaemia: A systematic review and economic evaluation. Health Technology Assessment 12:1-92. 2. Pandor A, Ara RM, Tumur I et al. (2009) Ezetimibe monotherapy for cholesterol lowering in 2,722 people: systematic review and meta-analysis of randomized controlled trials. Journal of Internal Medicine 265:568-580. 3. Bass A, Hinderliter AL, and Lee CR. (2009) The impact of ezetimibe on endothelial function and other markers of cardiovascular risk. Annals of Pharmacotherapy 43:2021-2030. 4. Kawashiri MA NA. (2008) Comparison of effects of pitavastatin and atorvastatin on plasma coenzyme Q10 in heterozygous familial hypercholesterolemia: results from a crossover study. Clinical pharmacology and therapeutics 83:731-739. 5. Nozue T, Michishita I, Ito Y et al. (2008) Effects of statin on small dense low-density lipoprotein cholesterol and remnant-like particle cholesterol in heterozygous familial hypercholesterolemia. Journal of Atherosclerosis & Thrombosis 15:146-153. 6. Marais AD RFSERDB. (2008) A dose-titration and comparative study of rosuvastatin and atorvastatin in patients with homozygous familial hypercholesterolaemia. Atherosclerosis 197:400-406. 7. Masoura C, Pitsavos C, Aznaouridis K et al. (2011) Arterial endothelial function and wall thickness in familial hypercholesterolemia and familial combined hyperlipidemia and the effect of statins. A systematic review and meta-analysis. Atherosclerosis 214:129-138. 8. Vergeer M, Zhou R, Bots ML et al. (1-7-2010) Carotid atherosclerosis progression in familial hypercholesterolemia patients: a pooled analysis of the ASAP, ENHANCE, RADIANCE 1, and CAPTIVATE studies. Circulation Cardiovascular:398-404. 9. Nherera L, Calvert NW, Demott K et al. (2010) Cost-effectiveness analysis of the use of a high-intensity statin compared to a low-intensity statin in the management of patients with familial hypercholesterolaemia. Current Medical Research & Opinion 26:529-536. 10. Browne B and Vasquez S. (2008) Pediatric dyslipidemias: Prescription medication efficacy and safety. Journal of Clinical Lipidology 2:189-201.

11. Shafiq N, Bhasin B, Pattanaik S et al. (2007) A meta-analysis to evaluate the efficacy of statins in children with familial hypercholesterolemia. International Journal of Clinical Pharmacology & Therapeutics 45:548-555.

12. Arambepola C, Farmer AJ, Perera R et al. (2007) Statin treatment for children and adolescents with heterozygous familial hypercholesterolaemia: a systematic review and meta-analysis. Atherosclerosis 195:339-347.

13. Cohen H, Stein-Zamir C, Hamiel O et al. (2010) Israeli guidelines for the management of hypercholesterolemia in children and adolescents. Report of the pediatric association expert group. e-SPEN 5:e132-e143.

14. O'Gorman CS, Higgins MF, and O'Neill MB. (2009) Systematic review and metaanalysis of statins for heterozygous familial hypercholesterolemia in children: evaluation of cholesterol changes and side effects. Pediatric Cardiology 30:482-489.

15. Vuorio A, Kuoppala J, Kovanen PT et al. (2010) Statins for children with familial hypercholesterolemia. Cochrane Database of Systematic Reviews CD006401.

16. Lebenthal Y, Horvath A, Dziechciarz P et al. (2010) Are treatment targets for hypercholesterolemia evidence based? Systematic review and meta-analysis of randomised controlled trials. Archives of Disease in Childhood 95:673-680.

17. Avis HJ HBG. (2010) Efficacy and safety of rosuvastatin therapy for children with familial hypercholesterolemia. Journal of the American College of Cardiology 55:1121-1126.

18. Ryu SK, Hutten BA, Vissers MN et al. (2011) Lipoprotein-associated phospholipase A2 mass and activity in children with heterozygous familial hypercholesterolemia and unaffected siblings: effect of pravastatin. Journal of Clinical Lipidology 5:50-56.

19. Davidson MH. (2011) A systematic review of bile acid sequestrant therapy in children with familial hypercholesterolemia. Journal of Clinical Lipidology 5:76-81.

20. Perry CM. (1-4-2010) Colesevelam: in pediatric patients with heterozygous familial hypercholesterolemia. Paediatric Drugs 12:133-140.

21. Stein EA MAS. (2010) Colesevelam hydrochloride: efficacy and safety in pediatric subjects with heterozygous familial hypercholesterolemia. The Journal of pediatrics 156:231-236.

22. Huang Y, Li W, Dong L et al. (2013) Effect of statin therapy on the progression of common carotid artery intima-media thickness: An updated systematic review and meta-analysis of randomized controlled trials. Journal of Atherosclerosis and Thrombosis.20 (1) (pp 108-121), 2013.Date of Publication: 2013. 108-121.

23. Vuorio A, Kuoppala J, Kovanen PT et al. (2014) Statins for children with familial hypercholesterolemia. SO: Cochrane Database of Systematic Reviews CD006401.

24. Stein EA, Honarpour N, Wasserman SM et al. (2013) Effect of the proprotein convertase subtilisin/kexin 9 monoclonal antibody, AMG 145, in homozygous familial hypercholesterolemia. Circulation 128:2113-2120.

25. Raal FJ, Scott R, Somaratne R et al. (2012) Low-density lipoprotein cholesterol-lowering effects of AMG 145, a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease in patients with heterozygous familial hypercholesterolemia: the Reduction of LDL-C with PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder (RUTHERFORD) randomized trial. Circulation 126:2408-2417.

26. Stroes E, Colquhoun D, Sullivan D et al. (2014) Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: the GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab. Journal of the American College of Cardiology 63:2541-2548.

Appendix D: Search strategy

D.1 Case-finding

Databases that were searched, together with the number of articles retrieved from each database are shown in table Table 20: Clinical search summary. The Medline and Medline in Process search strategy is shown in Table 21. The same strategy was translated for the other databases listed.

Table 20: Clinical search summary

Database	Date searched	Number retrieved
Cochrane Central Register of Controlled Trials (CENTRAL)	05/05/16	1203
Cochrane Database of Systematic Reviews (CDSR)	05/05/16	40
Database of Abstracts of Reviews of Effect (DARE) (legacy records)	05/05/16	6
Embase (Ovid)	05/05/16	8341
Health Technology Assessment (HTA Database)	05/05/16	5
MEDLINE (Ovid)	05/05/16	5612
MEDLINE In-Process (Ovid)	05/05/16	615
PubMed[c]	05/05/16	783

Table 21: Clinical search terms (Medline and Medline in Process)

Line number/Search term/Number retrieved
1 Hyperlipidemia, familial combined/ (728)
2 Hyperlipoproteinemia Type II/ (5582)
3 ((famil* or essential* or monogenic* or hereditar* or inherit* or heterozygous* or homozygous*) adj4 (hypercholest* or hyperlip* or cholest* or lipid* or FH)).tw. (12687)
4 (FH or HoFH or HeFH).tw. (5440)
5 Cholesterol, LDL/ or Receptors, LDL/ (30339)
6 (LDL* adj (cholester* or receptor* or lipoprotein*)).tw. (24729)
7 (low* adj1 densit* adj1 lipoprotein* adj1 (receptor* or cholesterol*)).tw. (22208)
8 (LDLR or LDL-R or LDL R or LDLC or LDL-C or LDL C).tw. (13734)
9 Apolipoprotein B-100/ (1735)
10 (Famili* adj2 apolipoprotein*).tw. (220)
11 ((Apolipoprotein* or Apo or Apo-) adj1 (B or B-100 or B100 or B 100) adj1 (deficien* or syndrom* or defectiv*)).tw. (240)
12 Hyperlipoproteinemia Type I/ or Apolipoprotein C-II/ (1088)
13 ((Apolipoprotein* or Apo or Apo-) adj1 (C or C-II or CII or C II or "C-2" or "C2" or "C 2") adj1 (deficien* or syndrom* or defectiv*)).tw. (21)
14 ((ApoC2 or ApoCII or ApoB) adj1 (deficien* or syndrom* or defectiv*)).tw. (65)
15 or/1-14 (72796)
16 Medical Records Systems, Computerized/ (18525)
17 Medical Records/ (63140)
18 Hospital Records/ (3195)
19 Databases, factual/ (51573)

Line number/Search term/Number retrieved
20 Registries/ (62395)
21 Medical Audit/ (15588)
22 ((gp or general practi* or doctor* or nurse* or physician* or primary care or secondary care or clinic* or patient* or medical* or hospital* or computer* or electronic* or clinical practice*) adj2 (note* or record* or database* or regist* or audit* or data or datalink)).tw. (324817)
23 (GPRD or CPRD).tw. (448)
24 Medical History Taking/ or anamnes*.tw. (25456)
25 ((patient* or case* or medic*) adj2 (histor* or identif* or find* or screen*)).tw. (210882)
26 ((famil* or parent* or grand* or relative* or relation*) adj2 (histor* or case* or tracing or trace* or screen* or identif*)).tw. (82595)
27 (Simon adj1 Broom*).tw. (34)
28 (Dutch Lipid adj2 (clinic* or network* or criteria* or diagnos* or score*)).tw. (25)
29 DLCNCS.tw. (2)
30 Make Early Diagnosis to Prevent Early Death.tw. (9)
31 MEDPED.tw. (21)
32 ((cardiac* or coronar* or stroke or myocardial infarction or MI or heart attack) adj2 (care* or facili* or team* or unit* or investigat*) adj2 (note* or record* or database* or regist* or audit* or data)).tw. (222)
33 Myocardial Ischaemia National Audit Project.tw. (32)
34 MINAP.tw. (42)
35 National Institute for Cardiovascular Outcomes Research.tw. (14)
36 NICOR.tw. (10)
37 QRESEARCH.tw. (69)
38 National Audit of Percutaneous Coronary Intervention.tw. (1)
39 PCI.tw. (14238)
40 National Adult Cardiac Surgery.tw. (17)
41 NACSA.tw. (1)
42 Health Survey for England.tw. (339)
43 ((Patholog* or biochemistr* or lab or laborator*) adj2 (note* or record* or database* or regist* or audit* or data)).tw. (25804)
44 Genetic testing/ (29356)
45 ((cascade* or genetic*) adj2 (test* or train* or screen*)).tw. (24752)
46 ((selectiv* or proband* or proposit* or risk factor* or program*) adj2 (screen* or test*)).tw. (31704)
47 or/16-46 (858551)
48 15 and 47 (6236)
49 Animals/ not Humans/ (4191697)
50 48 not 49 (6205)
51 Limit 50 to english language (5612

D.2 Diagnosis

Databases that were searched, together with the number of articles retrieved from each database are shown in Table 22: Clinical search summary. The Medline and Medline in Process search strategy is shown in Table 23. The same strategy was translated for the other databases listed.

Table 22: Clinical search summary

Databases	Date searched	No. retrieved
Cochrane Central Register of Controlled Trials (CENTRAL)	05/10/16	78

Cochrane Database of Systematic Reviews (CDSR)	05/10/16	4
Database of Abstracts of Reviews of Effect (DARE) (legacy records)	05/10/16	1
Embase (Ovid)	05/10/16	2246
Health Technology Assessment (HTA Database)	05/10/16	2
MEDLINE (Ovid)	05/10/16	938
MEDLINE In-Process (Ovid)	05/10/16	198
PubMed[d]	05/10/16	311

Table 23: Clinical search terms (Medline and Medline in Process)

Line number/Search term/Number retrieved
1 Hyperlipidemia, familial combined/ (732)
2 Hyperlipoproteinemia Type II/ (5749)
3 ((famil* or essential* or monogenic* or hereditar* or inherit* or heterozygous* or homozygous*) adj4 (hypercholest* or hyperlip* or cholest* or lipid* or FH)).tw. (13192)
4 (FH or HoFH or HeFH).tw. (5742)
5 Cholesterol, LDL/ or Receptors, LDL/ (31538)
6 (LDL* adj (cholester* or receptor* or lipoprotein*)).tw. (25495)
7 (low* adj1 densit* adj1 lipoprotein* adj1 (receptor* or cholesterol*)).tw. (23397)
8 (LDLR or LDL-R or LDL R or LDLC or LDL-C or LDL C).tw. (14573)
9 Apolipoprotein B-100/ (1816)
10 (Famili* adj2 apolipoprotein*).tw. (220)
11 ((Apolipoprotein* or Apo or Apo-) adj1 (B or B-100 or B100 or B 100) adj1 (deficien* or syndrom* or defectiv*)).tw. (240)
12 Hyperlipoproteinemia Type I/ or Apolipoprotein C-II/ (1109)
13 ((Apolipoprotein* or Apo or Apo-) adj1 (C or C-II or CII or C II or "C-2" or "C2" or "C 2") adj1 (deficien* or syndrom* or defectiv*)).tw. (21)
14 ((ApoC2 or ApoCII or ApoB) adj1 (deficien* or syndrom* or defectiv*)).tw. (66)
15 or/1-14 (75847)
16 (Simon adj1 Broom*).tw. (36)
17 (Dutch Lipid adj2 (clinic* or network* or criteria* or diagnos* or score*)).tw. (33)
18 Dutch score*.tw. (4)
19 (DLCNCS or DLCN).tw. (10)
20 ((famil* or parent* or grand* or relative* or relation*) adj2 (histor* or case* or tracing or trace* or screen* or identif*) adj2 (famil* or essential* or monogenic* or hereditar* or inherit* or heterozygous* or homozygous*) adj4 (hypercholest* or hyperlip* or cholest* or lipid* or FH)).tw. (1503)
21 ((famil* or parent* or grand* or relative* or relation*) adj2 (histor* or case* or tracing or trace* or screen* or identif*) adj2 (coronar* or Ischaemic* or ischemic*) adj2 heart* adj2 (diseas* or disorder*)).tw. (324)
22 Genetic testing/ (30939)
23 ((cascade* or genetic* or dna) adj2 (test* or train* or screen*)).tw. (35227)
24 (tendon xanthomata or xanthelasmas).tw. (124)
25 ((corneal* or senil*) adj1 arcus).tw. (211)
26 or/16-25 (59196)
27 15 and 26 (2154)
28 animals/ not humans/ (4292287)
29 27 not 28 (2142)
30 limit 29 to ed=20070101-20161006 (1001)
31 limit 30 to english language (938)

[d] Limit search to publisher[sb] and last 3 days only. Tips on searching PubMed here

D.3 Management (statin monotherapy)

Databases that were searched, together with the number of articles retrieved from each database are shown in Table 24. The Medline and Medline in Process search strategy is shown in Table 23. The same strategy was translated for the other databases listed.

Table 24: Clinical search summary

Databases	Date searched	No. retrieved
Cochrane Central Register of Controlled Trials (CENTRAL)	29/09/16	2134
Cochrane Database of Systematic Reviews (CDSR)	29/09/16	15
Database of Abstracts of Reviews of Effect (DARE) (legacy records)	29/09/16	34
Embase (Ovid)	29/09/16	4972
Health Technology Assessment (HTA Database)	29/09/16	0
MEDLINE (Ovid)	29/09/16	3082
MEDLINE In-Process (Ovid)	29/09/16	321
PubMed[e]	29/09/16	172

Table 25: Clinical search terms (Medline and Medline in Process)

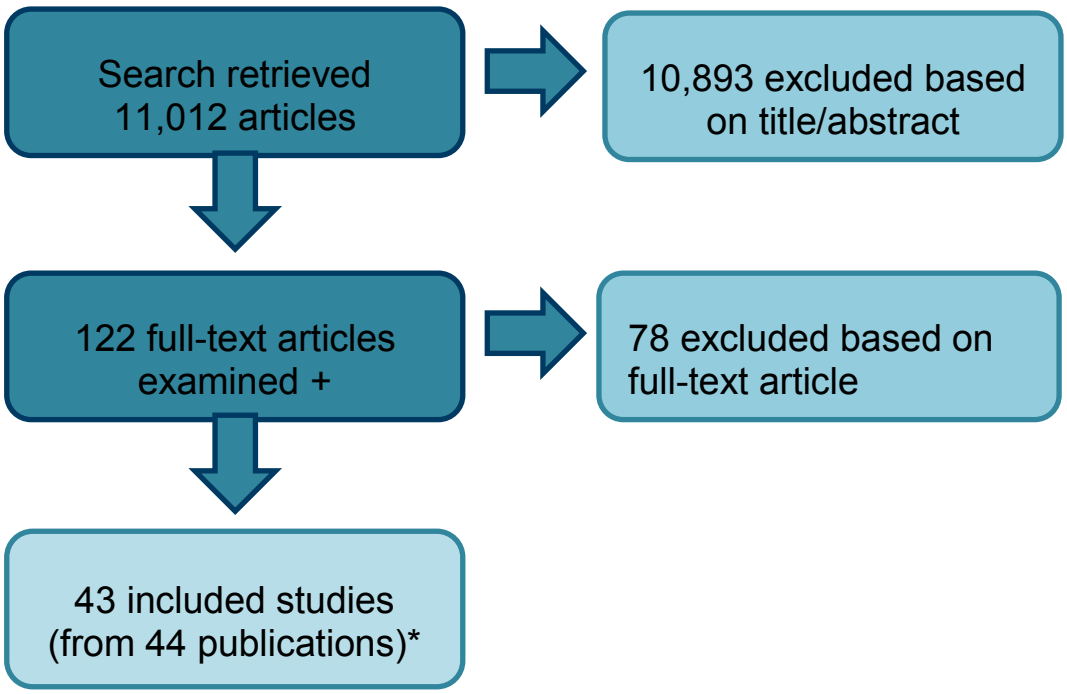
Line number/Search term/Number retrieved
1 Hyperlipidemia, familial combined/ (732)
2 Hyperlipoproteinemia Type II/ (5744)
3 ((famil* or essential* or monogenic* or hereditar* or inherit* or heterozygous* or homozygous*) adj4 (hypercholest* or hyperlip* or cholest* or lipid* or FH)).tw. (13163)
4 (FH or HoFH or HeFH).tw. (5729)
5 Cholesterol, LDL/ or Receptors, LDL/ (31478)
6 (LDL* adj (cholester* or receptor* or lipoprotein*)).tw. (25456)
7 (low* adj1 densit* adj1 lipoprotein* adj1 (receptor* or cholesterol*)).tw. (23332)
8 (LDLR or LDL-R or LDL R or LDLC or LDL-C or LDL C).tw. (14522)
9 Apolipoprotein B-100/ (1813)
10 (Famili* adj2 apolipoprotein*).tw. (220)
11 ((Apolipoprotein* or Apo or Apo-) adj1 (B or B-100 or B100 or B 100) adj1 (deficien* or syndrom* or defectiv*)).tw. (240)
12 Hyperlipoproteinemia Type I/ or Apolipoprotein C-II/ (1105)
13 ((Apolipoprotein* or Apo or Apo-) adj1 (C or C-II or CII or C II or "C-2" or "C2" or "C 2") adj1 (deficien* or syndrom* or defectiv*)).tw. (21)
14 ((ApoC2 or ApoCII or ApoB) adj1 (deficien* or syndrom* or defectiv*)).tw. (66)
15 or/1-14 (75700)
16 Atorvastatin Calcium/ (5539)
17 (Atorvastatin or Lipitor).tw. (6063)
18 Rosuvastatin Calcium/ (1958)
19 (Rosuvastatin or Crestor).tw. (2220)
20 Simvastatin/ or Ezetimibe, Simvastatin Drug Combination/ (6747)
21 (Simvador or Zocor or Inegy).tw. (112)
22 Pravastatin/ (3231)
23 (Statin* or Pravastatin).tw. (31316)
24 or/16-23 (38724)
25 15 and 24 (9237)

[e] Limit search to publisher[sb] and last 3 days only. Tips on searching PubMed here

Line number/Search term/Number retrieved
26 Randomized Controlled Trial.pt. (431498)
27 Controlled Clinical Trial.pt. (91725)
28 Clinical Trial.pt. (505774)
29 exp Clinical Trials as Topic/ (302612)
30 Placebos/ (33707)
31 Random Allocation/ (89038)
32 Double-Blind Method/ (139483)
33 Single-Blind Method/ (22859)
34 Cross-Over Studies/ (39679)
35 ((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw. (860218)
36 (random$ adj3 allocat$).tw. (24024)
37 placebo$.tw. (170178)
38 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (136594)
39 (crossover$ or (cross adj over$)).tw. (63097)
40 or/26-39 (1554896)
41 Meta-Analysis.pt. (73666)
42 Meta-Analysis as Topic/ (15408)
43 Review.pt. (2109968)
44 exp Review Literature as Topic/ (9095)
45 (metaanaly$ or metanaly$ or (meta adj3 analy$)).tw. (85278)
46 (review$ or overview$).ti. (316819)
47 (systematic$ adj5 (review$ or overview$)).tw. (80380)
48 ((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw. (5641)
49 ((studies or trial$) adj2 (review$ or overview$)).tw. (30076)
50 (integrat$ adj3 (research or review$ or literature)).tw. (6724)
51 (pool$ adj2 (analy$ or data)).tw. (18370)
52 (handsearch$ or (hand adj3 search$)).tw. (6907)
53 (manual$ adj3 search$).tw. (3860)
54 or/41-53 (2295137)
55 40 or 54 (3569304)
56 25 and 55 (6052)
57 Animals/ not Humans/ (4288026)
58 56 not 57 (5981)
59 limit 58 to ed=20070101-20160930 (3329)
60 limit 59 to english language (3082)

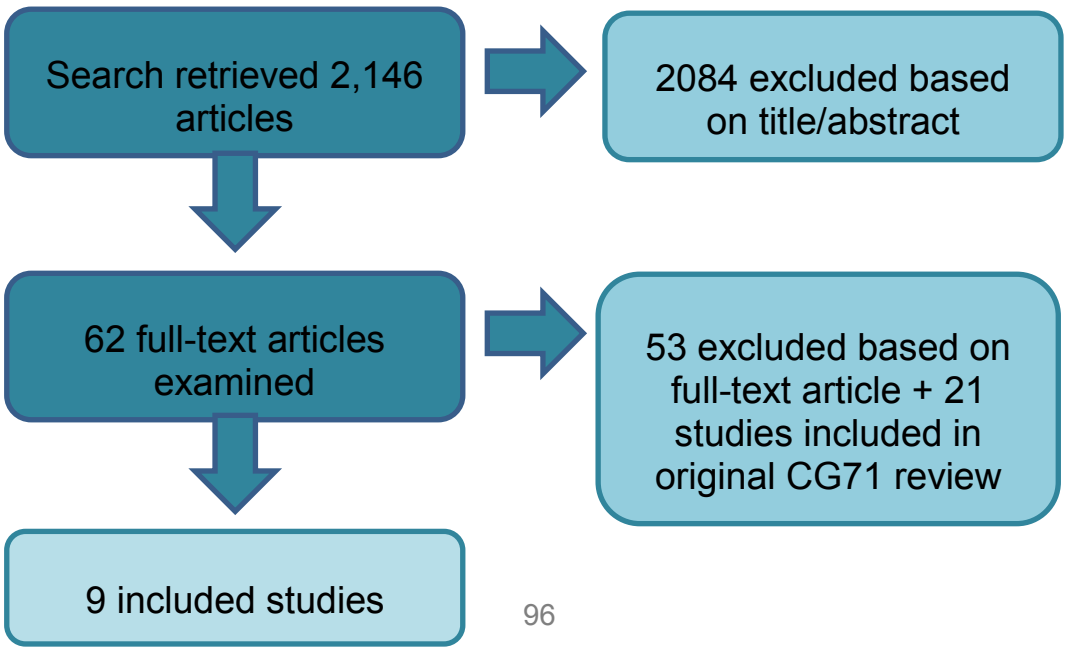
Appendix E: Review flowchart

E.1 Case-finding

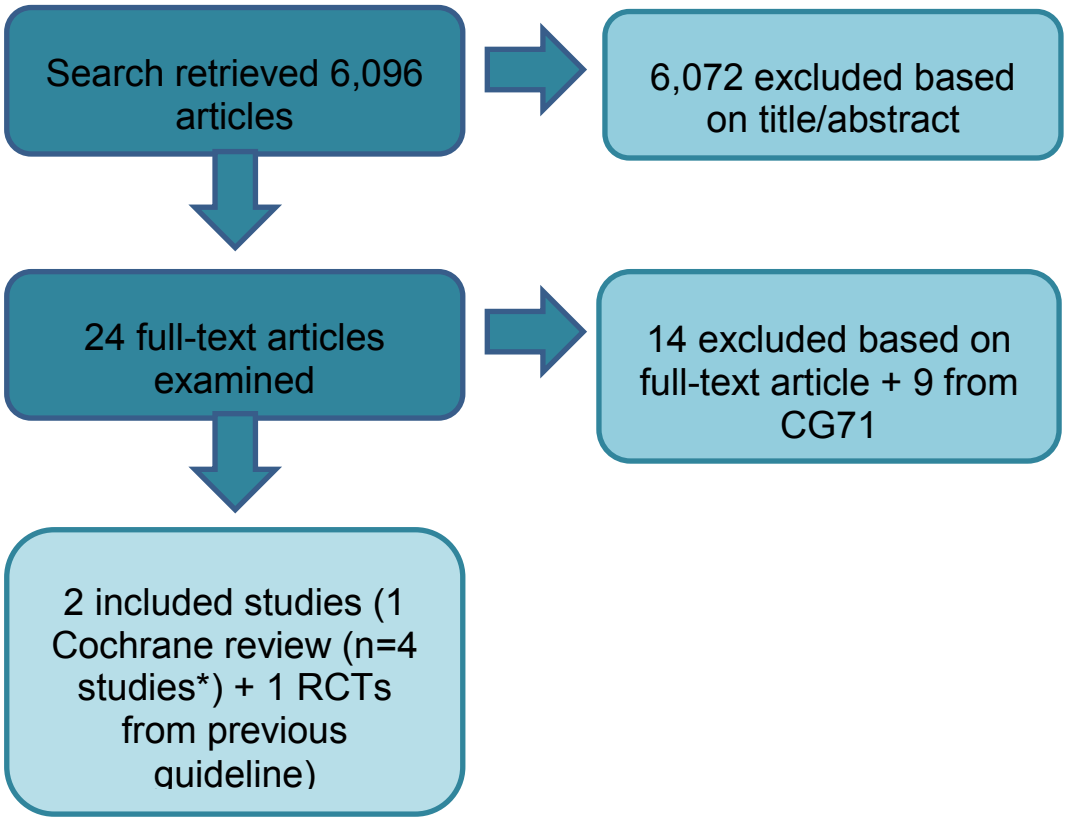


*including 5 of the 6 studies from the original guideline

E.2 Diagnosis



E.3 Management (statin monotherapy)



*Vuorio (2014) has 8 included studies; 4 excluded as used statins that are not licensed for use in children in the UK.

Appendix F:Excluded studies

F.1 Case finding

Reference	Reason for exclusion
Abaitua FR, Martinez JI, Lopez RE et al (1996). Family history as a predictor for childhood hyperlipidemia. Cardiovascular Risk Factors, 6, 277-83.	Incidence of hyperlipidaemia and hypercholesterolaemia, not FH
Alves A, Medeiros A, Francisco V et al (2009). Familial hypercholesterolaemia: A perspective of 10 years of study in Portugal. Atherosclerosis Supplements	Conference abstract
Anonymous . (1991). Risk of fatal coronary heart disease in familial hypercholesterolaemia. Scientific Steering Committee on behalf of the Simon Broome Register Group. BMJ, 303, 893-6.	Incidence of mortality in people with FH
Dennison BA, Jenkins PL and Pearson TA. (1994). Challenges to implementing the current pediatric cholesterol screening guidelines into practice. Pediatrics, 94, 296-302.	Study to identify children who should have cholesterol screened; assessing parental hypercholesterolaemia and family history of CHD
Bachman RP, Schoen EJ, Stembridge A et al (1993). Compliance with childhood cholesterol screening among members of a prepaid health plan. American Journal of Diseases of Children, 147, 382-5.	Assess compliance of parents/ children attending for cholesterol tests due to family history of hypercholesterolaemia
Bangert S K, Eldridge P H, and Peters T J. (1992). Neonatal screening for familial hypercholesterolaemia by immunoturbidimetric assay of apolipoprotein B in dried blood spots. Clinica Chimica Acta, 213, 95-101.	Study on method development for measurement of apolipoprotein B in dried blood spots
Bates T, Magana N, Chan H et al (2011). Predicting the yield of cascade screening for familial hypercholesterolaemia. Heart Lung and Circulation	Conference abstract
Bell MM, and Joseph S. (1990). Screening 1140 fifth graders for hypercholesterolemia: family history inadequate to predict results. Journal of the American Board of Family Practice, 3, 259-63.	Sensitivity and specificity of family history of high cholesterol or premature CVD to predict elevated cholesterol in child.
Bell D, Hooper A, Bender R et al (2012). Opportunistic screening for familial hypercholesterolaemia via a community laboratory. Heart Lung and Circulation, Conference	Conference abstract
Besseling J, Kindt I, Hof M et al (2014) Severe heterozygous familial hypercholesterolemia and risk for cardiovascular disease: a study of a cohort of 14,000 mutation carriers. Atherosclerosis. 2014 Mar;233(1):219-23	Risk of people with FH having a CV event
Besseling J, Huijgen R, Martin SS et al (2016). Clinical phenotype in relation to the distance-to-index-patient in familial hypercholesterolemia. Atherosclerosis, 246, 1-6.	Distance to index effect on LDL-C and CVD.
Besseling J, Reitsma JB, Gaudet D et al (2016). Selection of individuals for genetic testing for familial hypercholesterolaemia: development and external validation of a prediction model for the presence of a mutation causing familial hypercholesterolaemia. European Heart Journal ehw135	Development of model to predict presence of FH causing mutation in people referred by GPs
Bistritzer T, Batash D, Barr J et al (1996). Routine childhood screening for hyperlipidemia in Israel. Israel Journal of Medical Sciences, 32, 725-9.	No outcomes of interest

Reference	Reason for exclusion
Bogar MD, Basford JR, and Thomas RJ (2005). Rate and adequacy of cholesterol screening in patients admitted to a large rehabilitation unit after stroke. Archives of Physical Medicine & Rehabilitation, 86, 69-72.	Cholesterol screening in patients who have had a stroke; number on lipid lowering treatment prior to stroke
Boregowda K, Rice S, Grey B et al (2013). Screening for familial hypercholesterolaemia. In: Atherosclerosis. 27th Annual Conference of HEART UK 2013 Bristol University	Conference abstract
Boulton TJ (1979). The validity of screening for hypercholesterolaemia at different ages from 2 to 17 years. Australian and New Zealand Journal of Medicine, 9, 542-6.	Cases of hypercholesterolaemia and family history of CHD.
Calonge N, and Guirguis-Blake J. (2007). Screening for familial hypercholesterolaemia. BMJ, 335, 573-4.	Editorial
Catalan-Ramos A, Verdu JM, Grau M et al (2014). Population prevalence and control of cardiovascular risk factors: what electronic medical records tell us. Atencion Primaria, 46, 15-24.	Prevalence of cardiovascular risk factors in population. Not FH.
Datta BN, McDowell I F, and Rees A. (2010). Integrating provision of specialist lipid services with cascade testing for familial hypercholesterolaemia. Current Opinion in Lipidology, 21, 366-71.	Narrative review
Finnie RM. (2010). Cascade screening for familial hypercholesterolaemia in Scotland. British Journal of Diabetes and Vascular Disease, 10, 123-5.	Narrative review
Finnie RM, Bell C, Bloomfield P et al (2012). The first hundred families diagnosed with familial hypercholesterolaemia in two lipid clinics in Lothian. British Journal of Diabetes and Vascular Disease, 12, 243-7.	Reports number of different mutations found in people diagnosed with FH
Fouchier SW, Kastelein JJ, and Defesche JC (2005). Update of the molecular basis of familial hypercholesterolemia in The Netherlands. Human Mutation, 26, 550-6.	Description of molecular diagnoses of FH in Dutch registry; methods and mutations identified.
Galema-Boers JM, Versmissen J, Roeters van Lennep, HW et al (2015). Cascade screening of familial hypercholesterolemia must go on. Atherosclerosis, 242, 415-7.	All children had FH; assessing CVD in family history, % of patients with CVD incidence in parents and grandparents
Gidding SS, Whiteside P, Weaver S et al (1989). The child as proband. High prevalence of unrecognized and untreated hyperlipidemia in parents of hyperlipidemic children. Clinical Pediatrics, 28, 462-5.	Hyperlipidaemia in children and number of parents with hyperlipidaemia, not FH.
Griffin TC, Christoffel KK, Binns HJ et al (1989). Family history evaluation as a predictive screen for childhood hypercholesterolemia. Pediatric Practice Research Group. Pediatrics, 84, 365-73.	Sensitivity and PPV of family history in predicting LDL-C
Hadfield G S, and Humphries SE. (2007). Familial hypercholesterolaemia: Cascade testing is tried and tested and cost effective. BMJ, 335, 683.	Earlier report of Hadfield (2009) data; more up to date and relevant data in Hadfield (2009)
Herman K, Van Heyningen C, and Wile D. (2009). Cascade screening for familial hypercholesterolaemia and its effectiveness in the prevention of vascular disease. British Journal of Diabetes and Vascular Disease, 9, 171-74.	Non-systematic review
Humphries SE, and Hadfield G. (2008). Identifying patients with familial hypercholesterolaemia in primary care. Heart, 94, 695-6.	Editorial
Imtiaz F. (2009). Estimation of heritability of familial hypercholesterolemia among 335 family members of five	Does not report diagnostic yield of FH in relatives.

Reference	Reason for exclusion
hypercholesterolemic probands of Pakistani population. Journal of Ayub Medical College, and Abbottabad: JAMC, 21, 58-61.	
Kashani M, Eliasson A, Vernalis M et al (2015). A systematic approach incorporating family history improves identification of cardiovascular disease risk. Journal of Cardiovascular Nursing, 30, 292-7.	Family history of CVD, not familial hypercholesterolaemia.
Kastelein JJ. (2000). Screening for familial hypercholesterolaemia. Effective, safe treatments and dna testing make screening attractive. BMJ, 321, 1483-4.	Correspondence
Kirke A, Watts G F, and Emery J. (2012). Detecting familial hypercholesterolaemia in general practice. Australian Family Physician, 41, 965-8.	Narrative review with focus on management of FH in primary care
Kusters DM, de Beaufort C , Widhalm K et al (2012). Paediatric screening for hypercholesterolaemia in Europe. Archives of Disease in Childhood, 97, 272-6.	Narrative review on paediatric screening strategies
Marang-van de Mheen PJ, ten Asbroek AH, Bonneux L et al(2002). Cost-effectiveness of a family and DNA based screening programme on familial hypercholesterolaemia in The Netherlands. European Heart Journal, 23, 1922-30.	Cost effectiveness
Marks D, Wonderling D, Thorogood M et al. (2000) Screening for hypercholesterolaemia versus case finding for familial hypercholesterolaemia: a systematic review and cost effectiveness analysis. Health Technology Assessment; 4 (29) :1-123.	Review >5 yrs old.
Marks D, Wonderling D, Thorogood M et al 2002). Cost effectiveness analysis of different approaches of screening for familial hypercholesterolaemia. BMJ, 324, 1303.	Health economics paper
Marks D, Thorogood M, Neil HA et al (2003). Comparing costs and benefits over a 10 year period of strategies for familial hypercholesterolaemia screening. Journal of Public Health Medicine, 25, 47-52.	Health economics paper
Neely RD. (2014). The importance of early diagnosis: How to identify patients with FH for diagnosis and referral. Primary Care Cardiovascular Journal, 7, 31-5.	Narrative review
Neil H A, Hammond T, Huxley R et al (2000). Extent of underdiagnosis of familial hypercholesterolaemia in routine practice: prospective registry study. BMJ, 321, 148.	Short report on underdiagnosis of FH with insufficient detail to critically appraise.
Nherera L, Marks D, Minhas R et al (1175). Probabilistic cost-effectiveness analysis of cascade screening for familial hypercholesterolaemia using alternative diagnostic and identification strategies. Heart, 97, 1175-81.	Economic analysis
O'Loughlin J, Lauzon B, Paradis G et al (1723). Usefulness of the American Academy of Pediatrics recommendations for identifying youths with hypercholesterolemia. Pediatrics, 113, 1723-7.	Prevalence of hypercholesterolaemia, not focussed on FH
Pears R, Griffin M, Watson M et al (2014). The reduced cost of providing a nationally recognised service for familial hypercholesterolaemia. Open Heart, 1, e000015.	Economic analysis
Pears R, Griffin M, Futema M et al (2015). Improving the cost-effectiveness equation of cascade testing for familial hypercholesterolaemia. Current Opinion in Lipidology, 26, 162-8.	Opinion
Ramaswami U, Cooper J, and Humphries SE. (2016). The UK Paediatric Familial Hypercholesterolaemia Register: preliminary data. Archives of Diseases in Children	Description of demographics of children with FH. No detail on how identified.
Sazonov V, Beetsch J, Phatak H et al (2010). Association between dyslipidemia and vascular events in patients treated with	Association between high levels of HDL and

Reference	Reason for exclusion
statins: report from the UK General Practice Research Database. Atherosclerosis, 208, 210-6.	cardiovascular or cerebrovascular events in people with high concentration of LDL.
Skovby F, Micic S, Jepsen B et al. (1991). Screening for familial hypercholesterolaemia by measurement of apolipoproteins in capillary blood. Archives of Disease in Childhood, 66, 844-7.	Does not report yield of FH in relatives; unreliable/ unclear method of diagnosis of FH.
Staunton A, Vallance D T, Child A et al (1994). Unrecognized dyslipoproteinemia in United Kingdom families recruited to a genetic register because of unexplained coronary heart disease. Journal of Laboratory & Clinical Medicine, 123, 842-8.	No outcomes of interest: selected probands and relatives, incidence of FH not reported; study reports demographics and lipid profiles of population.
Starr B, Hadfield SG, Hutten BA et al (2008). Development of sensitive and specific age-and gender-specific low-density lipoprotein cholesterol cutoffs for diagnosis of first-degree relatives with familial hypercholesterolaemia in cascade testing. Clinical Chemistry & Laboratory Medicine, 46, 791-803.	Study focussed on formulation of age specific LDL cut-offs using Netherland FH data; validation of study-developed criteria through application to Danish and Norwegian datasets to assess sensitivity and specificity of new criteria.
Steyn K, Fourie J M, and Shepherd J. (1569). Detection and measurement of hypercholesterolaemia in South Africans attending general practitioners in private practice -The cholesterol monitor. South African Medical Journal, 88, 1569-74.	Survey of primary care practitioners, prevalence of reported FH only, no screening strategy.
Talmud P, Tybjaerg-Hansen A, Bhatnagar D et al (1991). Rapid screening for specific mutations in patients with a clinical diagnosis of familial hypercholesterolaemia. Atherosclerosis, 89, 137-41.	Development of specific DNA test for a FH mutation. Not a “whole population” screen, but looking for a specific phenotype and how mutation specific therapy may be developed for this mutation.
Talmud PJ, Shah S, Whittall R et al (2013). Use of low-density lipoprotein cholesterol gene score to distinguish patients with polygenic and monogenic familial hypercholesterolaemia: A case-control study. The Lancet, 381,1293-301.	Using LDL gene score to distinguish between monogenic and polygenic FH
ten Asbroek AH, de Mheen PJ, Defesche JC et al (2001). Results from a family and DNA based active identification programme for familial hypercholesterolaemia. Journal of Epidemiology & Community Health, 55, 500-2.	Analyses prevalence of FH and prevalence of mutations in those with FH
Tonstad S, Vollebaek LE and Ose L. (1995). Screening for familial hypercholesterolaemia in relatives. Lancet, 346, 1438.	Correspondence
Troxler RG, Park MK, Miller MA et al (1991). Predictive value of family history in detecting hypercholesterolemia in predominantly Hispanic adolescents. Texas Medicine, 87, 75-9.	Family history of premature CVD, predictive value of premature CVD in a parent on the total cholesterol level in child
Tyerman P F, and Tyerman G V. (2002). Another way of screening for familial hypercholesterolaemia. BMJ, 325, 340	Correspondence
Umans-Eckenhausen MA, Defesche JC, van Dam MJ et al (2003). Long-term compliance with lipid-lowering medication after genetic screening for familial hypercholesterolemia. Archives of Internal Medicine, 163, 65-8.	Follow up questionnaire to assess proportion of people diagnosed with FH receiving treatment

Reference	Reason for exclusion
van Aalst-Cohen ES, Jansen AC, Tanck MW et al (2006). Diagnosing familial hypercholesterolaemia: the relevance of genetic testing. European Heart Journal, 27, 2240-6.	Assesses clinical and biochemical differences in those with or without LDLR mutation.
van Maarle MC, Stouthard ME, and Bonsel GJ. (2003). Quality of life in a family based genetic cascade screening programme for familial hypercholesterolaemia: a longitudinal study among participants. Journal of Medical Genetics, 40, e3.	Quality of life outcomes for people undergoing FH screening
Wald D S, Bestwick JP, and Wald NJ. (2007). Child-parent screening for familial hypercholesterolaemia: screening strategy based on a meta-analysis. BMJ, 335, 599	Only reports mean TC or LDL; not an outcome of interest
Weng S F, Kai J, Andrew Neil, H , Humphries S E, and Qureshi N. (2015). Improving identification of familial hypercholesterolaemia in primary care: derivation and validation of the familial hypercholesterolaemia case ascertainment tool (FAMCAT). Atherosclerosis, 238, pp.336-43.	Validation of FH assessment tool; does not report outcomes of interest.
Wilcken DE, Blades BL and Dudman NP. (1988). A neonatal screening approach to the detection of familial hypercholesterolaemia and family-based coronary prevention. Journal of Inherited Metabolic Disease, 11 Suppl 1, 87-90.	Number of people with FH diagnosed not reported
Wilson C. (2013). Targeting cascade screening in familial hypercholesterolaemia. Nature Reviews Cardiology, 10,	Correspondence
Wonderling D, Umans-Eckenhausen MA et al (2004) Cost-effectiveness analysis of the genetic screening program for familial hypercholesterolemia in The Netherlands. Seminars in Vascular Medicine; 4 (1) :97-104.	Economic analysis

F.2 Diagnosis

Reference	Reason for exclusion
Agnieszka Wegrzyn, A , Fijalkowski M, Taszner M, Chmara M, Wasag B, Limon J, Rynkiewicz A, and Gruchala M. (2014). Familial hypercholesterolemia in Polish population-clinical and molecular diagnosis. European Journal of Preventive Cardiology, 21(1 SUPPL. 1), pp.S88.	Abstract
Ahmad Z S, Andersen R L, Andersen L H, O'Brien E C, Kindt I, Shrader P, Vasandani C, Newman C B, deGoma E M, Baum S J, Hemphill L C, Hudgins L C, Ahmed C D, Kullo I J, Gidding S S, Duffy D, Neal W, Wilemon K, Roe M T, Rader D J, Ballantyne C M, Linton M F, Duell P B, Shapiro M D, Moriarty P M, and Knowles J W. (2016). US physician practices for diagnosing familial hypercholesterolemia: data from the CASCADE-FH registry. Journal of Clinical Lipidology, 10(5), pp.1223-9.	Comparison of clinical scoring systems only: Simon Broome vs DLCN vs medped
Benlian P, Turquet A, Carrat F, Amsellem S, Sanchez L, Briffaut D, and Girardet J P. (2009). Diagnosis scoring for clinical identification of children with heterozygous familial hypercholesterolemia. Journal of Pediatric Gastroenterology & Nutrition, 48(4), pp.456-63.	Does not use Simon Broome or Dutch Lipid Clinic scoring system
Besseling J, Reitsma J B, Gaudet D, Brisson D, Kastelein J J, Hovingh G K, and Hutten B A. (2016). Selection of individuals for genetic testing for familial hypercholesterolaemia: development and external validation of a prediction model for the presence of a mutation causing familial hypercholesterolaemia. Eur Heart J, , pp..	Development of a model to predict presence of FH mutation. No DLCN or SB criteria used.
Bourbon M, Medeiros A M, Alves A C, Francisco V, Gaspar I M, Rato Q, Gaspar A, and Guerra A. (2010). Clinical diagnosis versus genetic diagnosis in familial hypercholesterolaemia. European Journal of Cardiovascular Prevention and Rehabilitation, 17, pp.S5.	Abstract

Reference	Reason for exclusion
Breen J, Jones J, and Barbir M. (2011). Genetic screening for familial hypercholesterolaemia in a cardiothoracic tertiary referral centre. Atherosclerosis, 218(2), pp.e5.	Abstract
Civeira F, Ros E, Jarauta E, Plana N, Zambon D, Puzo J, Martinez de Esteban, J P, Ferrando J, Zabala S, Almagro F, Gimeno J A, Masana L, and Pocovi M. (2008). Comparison of genetic versus clinical diagnosis in familial hypercholesterolemia. American Journal of Cardiology, 102(9), pp.1187-93, 1193.e1.	Only tests for mutations in LDLR and APOB genes, not PCSK9.
Cohen S S, Shirey-Rice J, Hardin J, et al. (2016). Identification of patients with familial hypercholesterolemia (FH) using the Dutch lipid network (DLN) criteria in electronic health records (EHR). Circulation, 133.	Abstract
Fabregate R, Fabregate M, Martinez C, et al. (2014). Result of genetic testing for diagnosis of LDLR and apob related heterozigous Familial Hypercholesterolemia (FH) in patients with clinical criteria. Journal of the American Society of Hypertension, 8(4 SUPPL. 1), e107.	Abstract
Finnie R M, Walker S, Simpson W G, and Miedzybrodzka Z. (2011). The first ninety families diagnosed with mutation positive familial hypercholesterolaemia in two lipid clinics in a Scottish Health Board area. Atherosclerosis, 218(2), pp.e3.	Abstract
Finnie R M, Bell C, Bloomfield P, Ho C K. M, Jenks S, Shand N, and Walker S W. (2012). The first hundred families diagnosed with familial hypercholesterolaemia in two lipid clinics in lothian. British Journal of Diabetes and Vascular Disease, 12(5), pp.243-247.	Analysis of distribution of mutations within genetically identified FH only. No clinical diagnosis undertaken.
Freiberger T, Plotena M, Zapletalova P, Goldmann R, Tichy L, and Fajkusova L. (2009). Familial hypercholesterolemia family screening in the Czech Republic. Atherosclerosis Supplements, 10(2), pp.no pagination.	Abstract
Freiberger T, Fajkusova L, Tichy L, Soska V, Ravcukova B, Ceska R, and Vrablik M. (2014). Fifteen years of active search for patients with familial hypercholesterolemia in the czech republic. Atherosclerosis, 235(2), pp.e197.	Abstract
Futema M, Whittall R, Wood G, Curtis M, McEwan J, and Humphries S E. (2011). Identification of patients with familial hypercholesterolaemia (FH) through the application of genetic testing in young mi patients from the MINAP register. Atherosclerosis, 218(2), pp.e5.	Abstract
Graesdal A, Ostli L, and Arnesen K E. (2009). Familial hypercholesterolemia in norway -Substantial variation in frequency of genetic testing and degree of follow up in different geographical regions. Atherosclerosis Supplements, 10(2), pp.no pagination.	Abstract
Grenkowitz T, Kassner U, Marz W, Binner P, Steinhagen-Thiessen E, and Demuth I. (2015). Mutation spectrum in German patients with familial hypercholesterolemia. Medizinische Genetik, 27(1), pp.127-128.	Foreign language paper
Grenkowitz T, Kassner U, Salewsky B, Marz W, Binner P, Steinhagen-Thiessen E, and Demuth I. (2016). Mutation spectrum in german patients with familial hypercholesterolemia-an update. Medizinische Genetik, 28(1), pp.152.	Foreign language paper
Haralambos K, Whatley S D, Datta B N, et al. (2013). Familial hypercholesterolaemia (FH) in Wales is genetically heterogeneous. Atherosclerosis, 231(2), pp.e2.	Abstract

Reference	Reason for exclusion
Haralambos K, Whatley S D, Edwards R, et al. (2014). Genetic variants of uncertain significance (VUS) in familial hypercholesterolaemia (FH): Can family based association studies help determine pathogenicity?. Atherosclerosis, 236(2), pp.e304.	Abstract
Ho C K, Stirling D, Hannant W, and Walker S W. (2012). Genetic mutations in patients with possible familial hypercholesterolaemia in South East Scotland. Scottish Medical Journal, 57(3), pp.148-51.	Comparison of clinical criteria to genetic testing: LDLR and APOB only.
Honeychurch J, Dean P, O'Shea S, et al. (2014). The impact of routine next generation sequencing testing for familial hypercholesterolaemia-8 months service experience. Clinical Chemistry and Laboratory Medicine, 52(11), eA340.	Abstract
Honeychurch J, Yarram-Smith L, O'Shea S, et al.(2014). Genetic testing of familial hypercholesterolaemia at BGL-a five year audit. Clinical Chemistry and Laboratory Medicine, 52(11), pp.eA340.	Abstract
Hooper A J, Nguyen L T, Burnett J R, et al (2009). Molecular screening approach for identification of mutations causing familial hypercholesterolaemia in Western Australia. Twin Research and Human Genetics, 12(2), 218.	Abstract
Huijgen R, Hutten B A, Kindt I, et al.. (2012). Discriminative ability of LDL-cholesterol to identify patients with familial hypercholesterolemia: a cross-sectional study in 26,406 individuals tested for genetic FH. Circulation. Cardiovascular Genetics, 5(3), 354-9.	All people had genetic testing for FH; no clinical diagnosis undertaken. Comparison of mutation and severity of LDL-C concentration.
Ibarretxe D, Feliu A, Ferre R, Merino J, Guijarro E, Andres P, Ramon R, Amigo E, Masana L, and Plana N. (2015). Heterozygous familial hypercholesterolemia detection in children: The decopin project. Atherosclerosis, 241(1), pp.e113.	Abstract
Langsted A, Kamstrup P R, Benn M, Tybjaerg-Hansen A, and Nordestgaard B G. (2016). High lipoprotein(a) as a possible cause of clinical familial hypercholesterolaemia: a prospective cohort study. The Lancet Diabetes & Endocrinology, 4(7), pp.577-87.	Association of mutation or clinical diagnosis with raised LDL-C levels; genetic analysis unclear, appears only to analyse mutations in LDLR and APOB.
Lee S, Shin D, Han S, Park S, Kang S, Jang Y, and Lee J. (2015). Clinical diagnosis of familial hypercholesterolemia in Korea: Comparison of mutation-prediction by simon broome-,Dutch, and MED/PED criteria. Atherosclerosis, 241(1), pp.e110-e111.	Abstract
Leren T P, Finborud T H, Manshaus T E, Ose L, and Berge K E. (2008). Diagnosis of familial hypercholesterolemia in general practice using clinical diagnostic criteria or genetic testing as part of cascade genetic screening. Community Genetics, 11(1), pp.26-35.	Only tests for mutations in LDLR and APOB. Unclear what clinical diagnosis used.
Lipworth L, Shirey-Rice J, Wei W Q., et al. (2015). Identification and characterization of heterozygous familial hypercholesterolemia patients using the Vanderbilt University medical center synthetic derivative database. European Heart Journal, 36,.927.	Poster
Lu C, Poulter E, Bates T.,et al. (2012). Assessment of the prevalence of familial hypercholesterolaemia in patients with premature coronary artery disease using three clinical tools. Heart Lung and Circulation, 21, S29-S30.	Abstract
Mabuchi H, Nohara A, Noguchi T, Kobayashi J, Kawashiri M A, Tada H, Yamagishi M, Inazu A, and Koizumi J. (2010). Usefulness of DNA analysisr the diagnosis of familial hypercholesterolemia (FH) and extraordinarily high frequency of FH in Japan. Atherosclerosis Supplements, 11(2), pp.115.	Abstract

Reference	Reason for exclusion
Maglio C, Mancina R M, Motta B M, Pirazzi C, Wiklund O, and Romeo S. (2014). Targeted next generation sequencing for genetic diagnosis of familial hypercholesterolemia. Atherosclerosis, 235(2), pp.e100.	Abstract
Mata N, Alonso R, Badiman L, et al. (2011). Clinical characteristics and evaluation of LDL-cholesterol treatment of the Spanish Familial Hypercholesterolemia Longitudinal Cohort Study (SAFEHEART). Lipids in Health and Disease, 10, pp.no pagination.	No detail on clinical diagnosis.
Medeiros AM, Alves AC, Francisco V et al (2010). Update of the Portuguese Familial Hypercholesterolaemia Study. Atherosclerosis, 212, 553-8.	
Medeiros A M, Alves A C, and Bourbon M. (2013). Mutational analysis of the portuguese cohort with clinical diagnosis of familial hypercholesterolemia. Cardiology (Switzerland), 126, pp.19.	Abstract
Medeiros A, Alves A, Aguiar P, and Bourbon M. (2014). APOB/apoA1 ratio improves clinical criteria sensitivity for the identification of FH children. Atherosclerosis, 235(2), pp.e64.	Abstract
Mickiewicz A, Chmara M, Futema M, Fijalkowski M, Chlebus K, Galaska R, Bandurski T, Pajkowski M, Zuk M, Wasag B, Limon J, Rynkiewicz A, and Gruchala M. (2016). Efficacy of clinical diagnostic criteria for familial hypercholesterolemia genetic testing in Poland. Atherosclerosis, 249, 52-8.	Does not test for all three mutations (LDLR, APOB and PCSK9); APOB and LDLR only.
O'Brien E C, DeGoma E, Moriarty P, et al.(2015). Initial results from the CASCADE-FH registry: CASCADE screening for awareness and detection of familial hypercholesterolemia. Journal of the American College of Cardiology, 65(10 SUPPL. 1), A1372.	Poster
Palacios L, Stef M, Taylor A et al. (2010). Rapid and accurate genetic diagnosis by LIPOchip in UK FH patients. Atherosclerosis Supplements, 11(2), 31.	Abstract
Poke S, Watts G, Maxwell S, Brameld K, and O'Leary P. (2009). Familial hypercholesterolaemia (FH) pilot cascade screening project. Twin Research and Human Genetics, 12(2), 229.	Abstract
Qureshi N, Weng S, and Tranter J. (2016). Erratum: Feasibility of improving identification of familial hypercholesterolaemia in general practice: Intervention development study (BMJ Open (2016) 6 (e011734)). BMJ Open, 6(6).	Erratum to Qureshi 2016
Qureshi N, Weng S, Tranter J, El-Kadiki A, and Kai J. (2016). Feasibility of improving identification of familial hypercholesterolaemia in general practice: intervention development study.[Erratum appears in BMJ Open. 2016;6(6):e011734corr1; PMID: 27338885]. BMJ Open, 6(5).e011734.	Unclear whether undertook genetic testing to confirm clinical diagnosis. No details of mutations tested for.
Raal F, Stein E A, Cariou B, et al. (2014). The diagnosis of heterozygous familial hypercholesterolemia: Genotype versus phenotype. Circulation, 130.	Abstract
Ruotolo A, D'Agostino M N, D'Angelo A, Di Taranto , M D, Guardamagna O, Malamisura B, De Matteo , A , Licenziati M R, Lenta S, Marotta G, and Fortunato G. (2014). Molecular diagnosis of familial hypercholesterolemia in pediatric cohort. Biochimica Clinica, 38(5), 512.	Not available from any sources.
Townsend D, Edmunds L, Gingell R, et al. (2013). Identification of familial hypercholesterolaemia within primary care-a collaborative approach with community GP networks. Atherosclerosis, 231(2),.e9-e10.	Abstract
Townsend D, Gingell R, Edwards R, et al. (2013). Initiation of a nurse led FH clinic for the identification of individuals with familial	Abstract

Reference	Reason for exclusion
hypercholesterolaemia (FH) in a rural setting. Atherosclerosis, 231(2), pp.e5-e6.	
van Aalst-Cohen , E S, Jansen A C, Tanck M W, Defesche J C, Trip M D, Lansberg P J, Stalenhoef A F, and Kastelein J J. (2006). Diagnosing familial hypercholesterolaemia: the relevance of genetic testing. European Heart Journal, 27(18), pp.2240-6.	Only tested for LDLR mutation in people with FH according to DLCN score.
Wald D S, Kasturiratne A, Godoy A, et al (2011). Child-parent screening for familial hypercholesterolemia. Journal of Pediatrics, 159(5), 865-7.	Meta-analysis of LDL-C concentration, incorrect intervention.
Wald D S, Bangash F A, and Bestwick J P. (2015). Prevalence of DNA-confirmed familial hypercholesterolaemia in young patients with myocardial infarction. European Journal of Internal Medicine, 26(2), pp.127-30.	No clinical diagnosis, genetic testing only.
Widhalm K, Dirisamer A, Lindemayr A, and Kostner G. (2007). Diagnosis of families with familial hypercholesterolaemia and/or APOB-100 defect by means of DNA analysis of LDL-receptor gene mutations. Journal of Inherited Metabolic Disease, 30(2), pp.239-47.	Used medped criteria – not in protocol; only assessed LDR receptor mutation.
Yarram L, Greenslade M, Bayly Get al. (2013). Genetic testing of familial hypercholesterolaemia at BGL-a four year audit. Atherosclerosis, 231(2), e2.	Abstract
Yarram-Smith L, Dean P, O'Shea S, et al. (2014). The impact of routine next generation sequencing testing for familial hypercholesterolaemia-5 months service experience. Atherosclerosis, 236(2),e304.	Abstract

F.3 Management (statin monotherapy)

Reference	Reason for exclusion
AstraZeneca . (2008). A phase IIIb, efficacy, and safety study of rosuvastatin in children and adolescents 10 to 17 years of age with heterozygous familial hypercholesterolemia (HeFH): a 12-week, double-blind, randomized, multicenter, placebo-controlled study with a 40-week, open-label, follow-up period. *Protocol D3561C00087 or 4522IL/0087*,	Protocol only
Avis H J, Hutten B A, Gagne C, Langslet G, McCrindle B W, Kastelein J J, and Stein E A. (2009). Efficacy and safety of rosuvastatin therapy for children with familial hypercholesterolemia: Results from the PLUTO study. *Journal of the American College of Cardiology*, 53(10), pp.A208.	Duplicate of Avis 2010 study (included)
Berthold H K, and Nitschmann S. (2008). [Therapy of familial hypercholesterolemia with or without ezetimibe]. *Der Internist*, 49(10), pp.1274-6.	Paper not in English
Braamskamp M J, Kusters D M, Avis H J, Wijburg F A, Kastelein J J, Wiegman A, and Hutten B A. (2013). Patients with familial hypercholesterolemia who initiated statin treatment in childhood are at lower risk for chd then their affected parents. *Circulation*, 128(22 suppl. 1), pp..	Abstract
Braamskamp M J, Tsimikas S, Wiegman A, Kastelein J J, and Hutten B A. (2013). Statin therapy and secretory phospholipase A2 in children with heterozygous familial hypercholesterolemia. *Atherosclerosis*, 229(2), pp.404-7.	No outcomes reported that match protocol.
Braamskamp M J, Kusters D M, Wiegman A, Avis H J, Wijburg F A, Kastelein J J, van Trotsenburg , A S, and Hutten B A. (2015). Gonadal steroids, gonadotropins and DHEAS in young adults with	Open label extension of RCT; no outcomes of interest reported.

Reference	Reason for exclusion
familial hypercholesterolemia who had initiated statin therapy in childhood. *Atherosclerosis*, 241(2), pp.427-32.	
Hernandez C, Francisco G, Ciudin A, Chacon P, Montoro B, Llaverias G, Blanco-Vaca F, and Simo R. (2011). Effect of atorvastatin on lipoprotein (a) and interleukin-10: A randomized placebo-controlled trial. [French]. *Diabetes & metabolism*, 37(2), pp.124-30.	Article not in English language
Kusters D M, Hutten B A, McCrindle B W, Cassiman D, Francis G A, Gagne C, Gaudet D, Morrison K M, Langslet G, Kastelein J J, and Wiegman A. (2013). Design and baseline data of a pediatric study with rosuvastatin in familial hypercholesterolemia. *Journal of Clinical Lipidology*, 7(5), pp.408-13.	Not an RCT
Lozano P, Henrikson N B, Dunn J, Morrison C C, Nguyen M, Blasi P R, Anderson M L, and Whitlock E P. (2016). Lipid Screening in Childhood and Adolescence for Detection of Familial Hypercholesterolemia: Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA*, 316(6), pp.645-55.	Systematic review on effectiveness of screening for FH
Perry C M. (2010). Colesevelam: in pediatric patients with heterozygous familial hypercholesterolemia. *Paediatric Drugs*, 12(2), pp.133-40.	Narrative report on Colesevelam
Pfizer Inc. (2011). A 1-year study in children and adolescents with familial or severe hypercholesterolemia comparing atorvastatin to placebo (6-month double-blind treatment), followed by atorvastatin open-label treatment for 6 months. *Protocol 981-147*, , pp..	Protocol only
Rodenburg J, Vissers M N, Wiegman A, van Trotsenburg , A S, van der Graaf , A , de Groot , E , Wijburg F A, Kastelein J J, and Hutten B A. (2007). Statin treatment in children with familial hypercholesterolemia: the younger, the better. *Circulation*, 116(6), pp.664-8.	Open label follow up of an RCT. All participants received statins.
Ryu S K, Hutten B A, Vissers M N, Wiegman A, Kastelein J J, and Tsimikas S. (2011). Lipoprotein-associated phospholipase A2 mass and activity in children with heterozygous familial hypercholesterolemia and unaffected siblings: effect of pravastatin. *Journal of Clinical Lipidology*, 5(1), pp.50-6	Open label extension of an RCT
Stein E A, Marais A D, Szamosi T, Raal F J, Schurr D, Urbina E M, Hopkins P N, Karki S, Xu J, Misir S, and Melino M. (2010). Colesevelam hydrochloride: efficacy and safety in pediatric subjects with heterozygous familial hypercholesterolemia. *Journal of Pediatrics*, 156(2), pp.231-6.e1-3	Incorrect intervention: colvesevalem
Stein E A, Dann E J, Wiegman A, Skovby F, Gaudet D, Sokal E, Charng M J, Mohamed M, Carlsson S, Raichlen J, and Kastelein J. (2016). A randomized, double-blind, placebo-controlled, multi-center, cross-over study of rosuvastatin in children and adolescents (aged 6 to <18 years) with homozygous familial hypercholesterolemia (HOFH). *Journal of the American College of Cardiology*, 67(13 SUPPL. 1), pp.1855	Population is people with Homozygous FH, excluded from review.
van der Graaf , A , Rodenburg J, Vissers M N, Hutten B A, Wiegman A, Trip M D, Stroes E S, Wijburg F A, Otvos J D, and Kastelein J J. (2008). Atherogenic lipoprotein particle size and concentrations and the effect of pravastatin in children with familial hypercholesterolemia. *Journal of Pediatrics*, 152(6), pp.873-8.	Incorrect study design: Case control study (siblings with FH vs unaffected siblings)
Vergeer M, Zhou R, Bots M L, Duivenvoorden R, Koglin J, Akdim F, Mitchel Y B, Huijgen R, Sapre A, de Groot , E , Sijbrands E J, Pasternak R C, Gagne C, Marais A D, Ballantyne C M, Isaacsohn J L, Stalenhoef A F, and Kastelein J J. (2010). Carotid atherosclerosis progression in familial hypercholesterolemia patients: a pooled	Pooled analysis of studies excluded from the review (not statin monotherapy intervention)

Reference	Reason for exclusion
analysis of the ASAP, ENHANCE, RADIANCE 1, and CAPTIVATE studies. *Circulation. Cardiovascular imaging*, 3(4), pp.398-404.	

Appendix G: Evidence tables

G.1 Case finding

G.1.1 Cascade testing

Bell 2015

Bibliographic reference	Bell 2015
Study type	Prospective
Aim	Investigate effectiveness of cascade testing family members of the first 100 index cases with genetically confirmed FH in centralised service in western Australia.
Patient characteristics	Relatives of index patients; 62% from primary care. Index cases:male n= 41/100; age (yrs) 47.0 (SD 15.8) [n=6 aged 1-16 yrs) Mutation positive relatives: male 91/188 (48.4%); age 37.6 (SD 19.6) yrs; 18.6% had tendon xanthoma Mutation negative relatives: male 87/178 (48.9%); age 35.6 (SD 19.2) yrs; none had tendon xanthoma
Number of patients	366 relatives of 100 index patients with genetically proven FH (with at least one family member had been genetically screened). Index cases diagnosed using DLNC. 6 index cases aged 10-16 yrs.
Index test	Genetic cascade testing (direct) Trained nurse contacted family members; firstly by letter then a 2nd letter or phone call if no response to 1st letter.
Reference standard (or Gold standard)	Lipid tests Genetic cascade testing (direct): APOB, LDLR, PCSK9
Time between testing & treatment	N/A
Length of follow-up	N/A
Location	Australia
Results	Index cases were diagnosed using Dutch Lipid Network Criteria. Family cascade testing initiated appropriate consent; trained nurse contacted family members. 8 declined testing.

Bibliographic reference	Bell 2015
	FH causing mutation found in 188 people (51.4%) 178 mutation negative
Source of funding	Not reported
Comments	Index patients diagnosed with DLNC, not clear whether they also had genetic testing. Demographics of mutation positive and negative relatives presented separately.

Bhatnager 2000

Bibliographic reference	Bhatnager 2000
Study type	Case finding among relatives of patients with FH
Aim	To assess the feasibility of detecting cases of heterozygous familial hypercholesterolaemia by using a nurse-led genetic register.
Patient characteristics	Relatives of probands aged 18 years and over, attending lipid clinics for the 1st time between 1987 and 1998, identified by using the Simon Broome criteria for diagnosis of FH.
Number of patients	259 probands (137 men, 122 women), 285 first degree relatives.
Index test	Probands identified using Simon Broome criteria. First degree relatives sent a standardised letter explaining reason why suspected that they may have FH. Either chose to see nurse at hospital, or attend GP practice. Results of relatives serum cholesterol test sent to GP explaining why test had been done and importance of results. Location of nearest lipid clinic provided when the test gave a positive result. Concentrations of serum cholesterol, HDL-C, triglycerides, LDL-C and lipoprotein were measured in all people.
Reference standard (or Gold standard)	N/A
Time between testing & treatment	N/A
Length of follow-up	N/A
Location	Two lipid clinics in central and south Manchester
Results	Of 262 probands identified, 259 agreed to participate. 216 had at least 1 living first degree relative, estimated to be 285 in total; 205 of these were tested. Results for cholesterol concentration available for 200 relatives. 121 (46 men, 75 women) proved positive.

Bibliographic reference	Bhatnager 2000
	79 had serum cholesterol less than 7.5 mmol/L
Source of funding	NHS research and development grant and NHS research and development levy.
Comments	No DNA detection methods for FH used. Male probands less likely to produce a cooperative relative than female proband (p<0.0005)

Hadfield 2009

Bibliographic reference	Hadfield 2009
Study type	Retrospective
Aim	To identify the effect of the implementation of systematic recording and tracing first-degree family members of people with FH.
Patient characteristics	Index cases 931 FH patients 643 index cases responded 2292 first degree relatives identified, 798 already tested so not contacted, 1494 contacted.
Number of patients	931 index cases contacted, 643 responded, 545 index cases provided details for family tracing. 2292 living first degree relatives (FDRs).
Index test	Retrospective audit of medical notes of known FH patients (diagnosed using SB criteria). Nurse led cascade testing and family tracing.
Reference standard (or Gold standard)	N/A: audit
Time between testing & treatment	N/A: no treatment
Length of follow-up	No follow up. Relatives who were diagnosed with FH were offered lifestyle advice and therapeutic options for the management of their hyperlipidaemia, as per normal practice
Location	London. Clinic sites Manchester, Nottingham, Birmingham, Surrey, Bournemouth
Results	**Diagnostic yield:** 219/1494 had likely FH (168/990 living within catchment area, 51/504 living outside the catchment area) (103 uncertain diagnosis, 445 unlikely FH) **Uptake rate of testing:** 643/931 index cases responded, 545 index cases provide information for family tracing (43 report all family members have been tested). 591/1494 FDRs come forward for testing (591/990 within catchment area, 78/504 outside of catchment area)

Bibliographic reference	Hadfield 2009

	Age in Y											
	0-14		15-24		25-34		35-44		45-54		55 and over	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
Upper limit of grey zone	**5.3**	**5.6**	**5.3**	**6.0**	**6.3**	**6.2**	**6.6**	**6.4**	**7.2**	**7.0**	**7.3**	**7.6**
	3.4	3.7	3.4	3.8	4.5	4.2	4.7	4.3	5.2	4.8	5.2	5.2
Lower limit of grey zone	**5.0**	**5.3**	**4.8**	5.4	**5.4**	**5.5**	**5.9**	**5.8**	**6.3**	**6.2**	**6.2**	**6.6**
	3.1	3.4	3.0	3.3	3.8	3.6	4.0	3.7	4.4	4.0	4.3	4.4

Source of funding	Department of Health, UK IDEAS genetics knowledge park, BHF grant.
Comments	Excluded FDRs that were known to have already been tested. Scored well on CASP QA tool.

Jannes 2015

Bibliographic reference	Jannes 2015
Study type	Prospective
Aim	To describe the clinical and genetic data obtained from cascade screening in a large Brazilian cohort.
Patient characteristics	Study participants were referred from: 1. Lipid clinics with a clinical suspicion of FH, 2. Subjects not from the lipid clinic but who had performed a cholesterol test for other reasons and presented or referred previous LDL-C concentrations of >5.4mmol/L for adults and >4.3mmol/L for children 3. Subjects referred directly to cascade screening due to elevated cholesterol levels.
Number of patients	248 index patients, 394 relatives
Index test	Genetic testing
Reference standard (or Gold standard)	Genetic testing: LDLR, APOB and PCSK9 mutation.

Bibliographic reference	Jannes 2015
Time between testing & treatment	N/A
Length of follow-up	N/A
Location	Brazil
Results	Trained nurse applied a questionnaire and performed physical examination. Presence of early coronary disease history in patients and family. Of 248 possible cases, 175 SB criteria and 190 DLNC answered questionnaires that contemplated FH diagnosis. All relatives with identified FH mutation referred to InCors Lipid Clinic outpatient unit. Index cases: 125/248 (50.4%) mutation positive (123 mutation negative) Relatives: 234/394 (59.4%) mutation positive (160 mutation negative) Sensitivity and specificity of DLNC and SB to detect FH mutation

DLNC	Mutation +ve, % (n)	Mutation – ve, % (n)	Sensitivity % (CI)	Specificity % (CI)	PPV % (CI)	NPV % (CI)
0-2 points	3.6 (3)	19.8 (18)				
3-5 – possible	19 (16)	36.3 (33)	96.4 (89.1-99)	19.7 (12.4-29.7)	52.5 (44.4-60.6)	85.7 (62.6-96.2)
6-8 probable	32.1 (27)	31.9 (29)	77.3 (66.7-85.5)	56.0 (45.2-66.3)	61.9 (51.8-71.0)	72.8 (60.7-82.4)
>8 definitive	45.2 (38)	12.1 (11)	45.2 (34.4-56.4)	87.9 (78.9-93.5)	77.5 (63.0-87.7)	63.4 (54.3-71.7)
total	100 (84)	100 (91)				

SB	Mutation +ve, % (n)	Mutation –ve, % (n)	Sensitivity % (CI)	Specificity % (CI)	PPV % (CI)	NPV % (CI)

Bibliographic reference	Jannes 2015						
	Definitive	10.5 (8)	0	10.5 (4.9-20.2)	10.5 (95.9-100)	100 (59.7-100)	62.6 (55.1-69.5)
	Probable	73.7 (56)	48.2 (55)	84.2 (73.6-91.2)	51.7 (42.2-61.1)	53.7 (44.4-62.8)	83.0 (71.9-90.5)
	No	15.8 (12)	51.8 (59)				
	Total	100 (76)	100 (114)				
Source of funding	Sociedade Hospital Samaritano and Ministerio da Saude.						
Comments	Sensitivity and specificity data for DLNC and SB to detect mutation not carried out on whole cohort. Only n=175 for DLNC and n=190 for SB data. Unclear why not all included participants included in analysis.						

Lee 1998

Bibliographic reference	Lee 1998
Study type	Prospective cohort
Aim	To track the LDL receptor gene in individual families with phenotypic FH and to identify and characterise any mutations of the LDLR gene that may be common in the west of Scotland FH population.
Patient characteristics	Patients with familial defective ApoB excluded by testing for ApoB-3500
Number of patients	80 probands, 200 relatives of probands and 50 normal controls
Index test	Clinical criteria for FH were: Fasting TC >9mmol/L, LDLC >7mmol/L plus one of the following: -strong family history of CHD -presence of either tendon xanthoma or xanthelasma -personal history of heart disease
Reference standard (or Gold standard)	Genetic test: LDLR gene only.
Time between testing & treatment	N/A
Length of follow-up	N/A
Location	Scotland
Results	3 probands had C163Y mutation 8 relatives had mutation and raised serum cholesterol

Bibliographic reference	Lee 1998
Source of funding	Not reported
Comments	Only tracking a specific mutation in LDLR gene only No baseline demographics reported. Study differs in numbers of mutations reported in different figures compared to text: Table 1 reports 7 probands with mutation and 11 relatives with mutatio

Leren 2008

Bibliographic reference	Leren 2008
Study type	Prospective cohort
Aim	Experience of the use of genetic cascade testing in Norway to diagnose FH patients
Patient characteristics	1st degree relatives of patients with molecularly defined FH consented to genetic cascade screening; 53% male 1415/1805 were 18 yrs or older
Number of patients	2472 relatives of 440 index patients
Index test	Genetic testing: LDLR and APOB
Reference standard (or Gold standard)	N/A
Time between testing & treatment	N/A
Length of follow-up	Additional questionnaire at 6 months follow up
Location	Norway
Results	Uptake:1805 (73%) blood samples received Diagnostic yield: 808/1805 (44.8%) mutation carriers, 997 had no mutation. 357/808 on lipid lowering therapy at time of testing Questionnaire 1062 adult relatives returned questionnaire (75.1%) 970 had TC measured 551 had elevated TC 209/551 (37.9%) had clinical diagnosis of FH

Bibliographic reference	Leren 2008
	184/209 had clinical and molecular diagnosis of FH Assuming that no person with low or normal serum cholesterol had been given a diagnosis of clinical FH, 46.2% (193/418) with molecularly defined FH would have been diagnosed by clinical criteria in general practice. Data indicated that a clinical diagnosis of FH in general practice has a sensitivity of 46.2% and specificity of 88.0% At 6 months; questionnaire sent to mutation carriers 10 years and older. 768 mutation carriers had been contacted and 361 (47%) have returned questionnaire along with a blood sample. 61.6% of mutation carriers on lipid lowering drugs at time of genetic testing 79% on lipid lowering therapy at 6 month follow up
Source of funding	Not reported
Comments	PCSK9 mutation not tested for. Unclear what clinical criteria used when FH clinically diagnosed.

Marks 2006

Bibliographic reference	Marks 2006
Study type	Case finding (secondary care)
Aim	To determine the proportion of cases of heterozygous FH would be identified by cascade screening conducted by a specialist hospital clinic.
Patient characteristics	227 eligible adult index cases, with 1075 first degree relatives. 225 eligible adult relatives.117 eligible children (<18 years)
Number of patients	Hospital clinic serving a population of 605,900 in Oxfordshire, UK 354 patients currently or previously attending the Oxford lipid clinic and meeting the diagnostic criteria of the Simon Broome Familial Hyperlipidaemia Register for definite or possible familial hypercholesterolaemia were identified by January 2002, after excluding 22 cases managed exclusively in primary care. 48 of the 354 were children aged under 18 years.
Index test	Using either pre-treatment measurements or the highest measurement on treatment, definite familial hypercholesterolaemia was defined as: (1) a total cholesterol concentration >7.5 mmol/L in adults (>6.7 mmol/L in children under 16 years) or an LDL cholesterol concentration >4.9 mmol/L in adults (>4.0 mmol/L in children), plus (2) tendon xanthomata in the patient or a first-or second-degree relative. A possible diagnosis of familial hypercholesterolaemia required the first definition above plus one of the following: (1) family history of myocardial infarction before age 50 years in second-degree relative or before age 60 years

Bibliographic reference	Marks 2006
	in first-degree relative, or (2) family history of raised total cholesterol concentration above 7.5 mmol/L in first-or second-degree relative. Total cholesterol concentration was measured on a non-fasting finger-prick capillary blood sample using a Cholestech LDX analyser (CholestechCorporation, Hayward, CA, USA) with a coefficient of variation of 4.9%.17 Those with diagnostic or borderline results were advised to have a confirmatory fasting venous specimen taken.
Reference standard (or Gold standard)	Results classified by US MedPed (Make Early Diagnosis Prevent Early Death) Program criteria using age-specific total cholesterol cut-points (age o20 years 5.7 mmol/L; 20–29 years 6.2 mmol/L; 30–39 years 7.0 mmol/L; and 40*þ* years 7.5 mmol/L)
Time between testing & treatment	N/A
Length of follow-up	N/A
Location	Oxfordshire, England
Results	227 adult index cases had 1075 first degree relatives – 442 adults (41%) and 117 children (11%) aged less than 18 yrs lived in Oxfordshire. 171 previously screened unaffected adults and 46 (too ill or elderly and infirm) were excluded 225 eligible adult relatives 28 responders (12%) planned to consult their general practitioner and 52 (23%) attended the clinic for testing. Parents of 113 children (97%) asked for their children to be tested and, with the exception of three families, all the parents asked for the tests to be done at home. The positive diagnostic rate was 29% (15/52) in adults and 32% (36/113) in children. Based on the population of Oxfordshire at the 2001 census, cascade screening increased the prevalence by 14.4% from 0.58/1000 (95% CI 0.52–0.65) to 0.67/1000 (95% CI 0.60–0.73), which represents a detection rate of 33.5% based on the estimated gene frequency of 2/1000.
Source of funding	Hyperlipidaemia education and research trust (Heart UK) and Pfizer SEH is funded by the British Heart Foundation and in part by a grant from the Department of Health to the London Genetics Knowledge Park.
Comments	Please see additional figure for this paper at the end of this evidence table document Good paper – many of the boxes ticked yes in the CASP tool. Just not sure about the confounding factors. Cascade testing relies on index patients providing all and the correct information. Some relatives may have been missed using this method.

Muir 2010

Bibliographic reference	Muir 2010
Study type	Case series
Aim	To identify the dianostic and treatment rates for FH in New Zealand.
Patient characteristics	588 people, out of a possible 10,500 affected people, who presented with a pre-treatment cholesterol _8.0 mmol/L, lipid stigmata or a strong family history of cardiovascular disease (CVD),
Number of patients	588 people referred for mutation screening; 76 index cases identified; 353 relatives screened.
Index test	DNA testing of LDLR gene
Reference standard (or Gold standard)	N/A
Time between testing & treatment	N/A
Length of follow-up	N/A
Location	New Zealand
Results	Between 2004 and 2008, 588 people were identified from pathology laboratory database were DNA tested for FH if they had TC >8 mmol/L (pre-treatment); lipid stigmata or a strong family history of CVD. 76 index cases identified from path lab database. Cascade testing: Patients with an identified mutation referred to clinical nurse specialist at CDHB lipid clinic for cascade testing. 95 patients with a severe phenotype who met criteria for mutation analysis but did not have an identified mutation, were also referred. All index patients provided contact details for their relatives who were sent letters explaining FH, consent forms and laboratory request forms.
Source of funding	None reported.
Comments	Not clear how many people were invited to cascade screening, unable to calculate uptake rate.

Norsworthy 2014

Bibliographic reference	Norsworthy 2014
Study type	Generation Scotland: Scottish Family Health study (pathology database)

Bibliographic reference	Norsworthy 2014
Aim	Targeted use of next generation sequencing as a potential route to diagnosis of FH in primary care population subset selected for hypercholesterolaemia. Cascade testing using molecular diagnostics.
Patient characteristics	Biological samples were obtained from the 'Generation Scotland: Scottish family Health study (GS:SFHS). Samples collected were from patients who were likely to have FH, based on previously reported population total cholesterol data in FH. Age and BMI thresholds were also used to reduce the inclusion of age and obesity related cases of hyperlipidaemia.
Number of patients	617 (selected on basis of total cholesterol data).
Index test	Genetic testing for FH. Patients were selected from the cohort using searches for TC, age and BMI cut-offs, termed the "High cholesterol group" (TC >8.5 mmol/L, TC 8-8.4mmol/L age <50 yrs, TC 8-8.4 mmol/L / age >50/ bmi <25, TC 7-7.9 mmol/L/ age <40) A cholesterol therapy group was selected (moderately high cholesterol despite lipid lowering therapy), and a control group.
Reference standard (or Gold standard)	N/A
Time between testing & treatment	N/A
Length of follow-up	N/A
Location	Scotland
Results	**Diagnostic yield** **FH causing mutations identified through testing in :** 4/193 (2.1%) of subjects in high cholesterol group 5/232 (2.2%) in cholesterol therapy group 0/192 in normocholesterolaemic group **Cascade testing:** DNA available for cascade testing in relatives of 6/9 (66%) index cases identified. 12 available first degree relatives (FDRs) 5 molecular diagnoses of FH were made.
Source of funding	Generation Scotland has received core funding from the Chief Scientist Office of the Scottish Government Health Directorates CZD/16/6 and the Scottish Funding Council HR03006. We also acknowledge funding from the MRC Clinical Sciences Centre and the British Heart Foundation to TJA, from a Wellcome Trust Clinical Training Fellowship to ERAT, and from the NIHR-funded Imperial Biomedical Research Centre to TJA.
Comments	Data for LDL-C ot reported in this study

Stempel 2016

Bibliographic reference	Stempel 2016
Study type	Retrospective review and prospective
Aim	To describe indications for initial cholesterol screening and examine outcomes of cascade screening efforts in family members of children with FH
Patient characteristics	42 paediatric patients from 34 unrelated families. 9 had existing diagnosis of FH. 55% male, mean age 10.4 years (range 6.1 – 20.2 years)
Number of patients	N=42, n=30 identified as families proband.
Index test	<18 years with LDLC ≥160mg/dL (22.2 mmol/L) on 2 lipid profiles, when a family history of high LDLC or premature CVD was identified in a parent of grandparent. Or, With LDLC ≥190mg/dL (26.4 mmol/L) on 2 lipid profiles when a family history unknown or incomplete. >18 years old with personal or family history of premature CVD with LDL-C ≥190mg/dL(26.4 mmol/L)
Reference standard (or Gold standard)	N/A
Time between testing & treatment	N/A
Length of follow-up	N/A
Location	USA
Results	Provider obtained family history and discussed cacade screening with parents. Parents obtained cholesterol results for themselves and family members to share with providers. If family member deceased and cause of death was premature cardiovascular disease, given a presumptive diagnosis of FH, Cascade screening led to 63 new diagnoses in relatives of children 58/63 were adults 5/63 were siblings of probands
Source of funding	Not reported
Comments	None

Taylor 1993

Bibliographic reference	Taylor 1993
Study type	Prospective cohort
Aim	To evaluate a more effective method of identifying children with FH by screening a population high a risk.

Bibliographic reference	Taylor 1993
Patient characteristics	200 children who were 1st or second degree relatives of people with premature onset coronary artery disease (120 families).
Number of patients	200 children identified from 120 families.
Index test	People with premature CAD (previous MI or angina) <50 yrs men, <55 yrs women considered as index cases, families approached by a health visitor via a GP.
Reference standard (or Gold standard)	Not detailed
Time between testing & treatment	No treatment given
Length of follow-up	6 months if diagnosed with FH
Location	Sheffield, UK
Results	12/200 new cases of FH (Diagnostic criteria: history of early CAD in 1st or 2nd degree relative, fasting TC of >5.9 mmol/L, HDL cholesterol <1.5 mmol/L, LDL-C >3.5 mmol/L, normal fasting triglyceride values (<2.3 mmol/L). the risk of developing ischaemic heart disease in children with confirmed hypercholesterolaemia calculated from ratio of total: HDL cholesterol.)

Case No	Age (years)	Total cholesterol	Triglyceride (mmol/l)	HDL cholesterol (mmol/l)	LDL cholesterol (mmol/l)
1	12.4	5 8**	0.5	1.3	4.27
2	7.4	7.7	0.9	0.84	6.45
3	4.7	8.2	1.2	0.81	6.84
4	12.0	6.4	1.0	1.26	4.14
5	10.2	5.7**	0.8	1.37	3.96
6	1.4*	11.1	1.8	0.53	9.75
7	11.7	6.4	0.9	1.16	4.23

Bibliographic reference	Taylor 1993

8	5.9	9.5	0.6	0.84	8.39
9	3.3	7.1	0.7	0.95	5.83
10	15.8	8.9	1.1	1.26	7.14
11	9.3	6.6	0.9	1.33	4.86
12	1.0*	9.8	1.5	1.02	8.10
*Children under 2 years not sampled unless siblings of known patient. **Previous total cholesterol >5 9 mmol/l.					

Source of funding	Not reported
Comments	CASP – can't tell whether authors have identified all confounding factors or whether they have taken account of the confounding factors in the design and/or analysis. It also wasn't clear whether the follow up of the subjects was complete or complete enough. Paper didn't contain any CI's to show how precise the results were. More research needed to show how the results will impact on practice.

Thorsson 2003

Bibliographic reference	Thorsson 2003
Study type	Prospective
Aim	Novel approach to systematic family screening compared to conventional proband screening for patients in Iceland.
Patient characteristics	Affected males: n=37), non-affected n=125; affected females n=26, non-affected n= 136.

	Males		Females	
	Affected male (n=37)	Nonaffected male (n=125)	Affected female (n=26)	Nonaffected female (n=136)
TC	9.5 (1.9)	5.6 (1.0)	9.4 (2.3)	5.9 (1.3)
HDL	1.0 (0.3)	1.2 (0.5)	1.2 (0.2)	1.5 (0.4)
TG	1.4 (0.9)	1.4 (0.8)	1.1 (0.6)	1.3 (0.6)

Number of patients	364 key individuals. 78 offspring of positive key individuals.
Index test	Clinical criteria used to identify probands:

Bibliographic reference	Thorsson 2003
	TC >8.5mmol/L in the proband and a first degree relative, tendon xanthoma in proband or first degree relative, myocardial infarction in proband or first degree relative before the age of 55 years.
Reference standard (or Gold standard)	Genetic testing: Only probands with the common mutation identified in Iceland (14T+2C) were included. Family tracing partly from computerised database derived from censuses (first carried out 1703), church records and birth and marriage certificates). Once a common ancestor was identified a list of all descendants was produced. The oldest individual was identified in a key individual and was contacted for cholesterol measurements and genetic testing. If positive for genetic testing, offspring were recruited for testing.
Time between testing & treatment	N/A
Length of follow-up	N/A
Location	Iceland
Results	2201 living individuals in 4 family clusters 364 key individuals identified 306 responded 35/306 (11%) key individuals who responded were positive for common mutation. Of 35 key individuals who were positive, 7 had not been previously diagnosed. Genealogical tracing identified 78 living offspring of positive key individuals. 68 were recruited 40 (59%) of these were positive 21 had already been diagnosed with FH, 19 had not been diagnosed previously and were not receiving lipid lowering therapy. 14 individuals of 75 FH patients identified in the families were from previously unknown family lineages.
Source of funding	Icelandic research council
Comments	Lack of baseline characteristics Unclear what the conventional proband screening method was Study has limited applicability to UK population because of the screening methods used.

Umans-Eckenhausen 2001

Bibliographic reference	Umans-Eckenhausen 2001
Study type	Case finding among relatives of patients with FH

<table>
<tr><th>Bibliographic reference</th><th>Umans-Eckenhausen 2001</th></tr>
<tr><td>Aim</td><td>Case finding programme to for individuals with FH, based on family investigation and DNA testing</td></tr>
<tr><td>Patient characteristics</td><td>Relatives of patients diagnosed with FH who are carriers of the mutation that causes FH.
<u>Age</u>
<40 n = 2678
40-59 n = 1819</td></tr>
<tr><td>Number of patients</td><td>1994-1998, 5442 people were enrolled into the identification programme.
Carriers of the genetic mutation n = 2039
Non carriers of the genetic mutation n = 3403</td></tr>
<tr><td>Index test</td><td>Family members of patients diagnosed with FH (index-cases) receive an information brochure describing the nature of FH by mail; they are then telephoned by a Genetic Field Worker (GFW) where the purpose of the screening programme is explained. GFW conducts a house visit with as many as possible family members present. Consent, health questionnaire conducted, names and addresses of family members to be contacted to be contacted later, and blood taken. Blood analysed for the presence of the mutation causing FH and total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides tested.</td></tr>
<tr><td>Reference standard (or Gold standard)</td><td>Not defined</td></tr>
<tr><td>Time between testing & treatment</td><td>Not defined</td></tr>
<tr><td>Length of follow-up</td><td>Index patients were usually seen for an additional 1 or 2 follow up visits – time not specified.</td></tr>
<tr><td>Location</td><td>Identification: The Amsterdam lipid research clinic at the medical centre of the University of Amsterdam and the Slotevaart University teaching hospital.
Screening: patients homes and at 1 of 75 lipid clinics in Amsterdam</td></tr>
<tr><td>Results</td><td>5442 index patients agreed to participate in the study.
<table>
<tr><td>Characteristics</td><td>Carriers</td><td>Noncarriers</td><td>P</td></tr>
<tr><td>n</td><td>2039 9 (37.5%)</td><td>3403 (62.5%)</td><td></td></tr>
<tr><td colspan="4">Age distribution (years)</td></tr>
<tr><td><40</td><td>1189 (58.3%)</td><td>1489 (43.7%)</td><td><.001</td></tr>
<tr><td>40-59</td><td>559 (27.4%)</td><td>1260 (37.0%)</td><td><.001</td></tr>
<tr><td colspan="4">Additional data in adults</td></tr>
<tr><td>Positive history of cardiovascular disease</td><td>186 (10.7%)</td><td>189 (6.0%)</td><td><.001</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Umans-Eckenhausen 2001			
	Previously known TC >290 mg/dL	875 (50.5%)	289 (9.4%)	*
	Treatment with statins	667 (38.5%)	160 (5.2%)	*
	Lipoproteins			
	Total cholesterol ± SD (mg/dL)	287 ± 64	212 ± 52	*
	LDL-cholesterol ± SD (mg/dL)	217 ± 61	137 ± 43	*
	HDL cholesterol ± SD (mg/dL)	42 ± 13	46 ± 14	*
	Triglycerides ± SD (mg/dL)	130 ± 95	147 ± 97	*
Source of funding	The research was supported with grants from the Dutch Ministry of Public Health, Welfare and Sport; the Health and Care Insurance Council; the Netherlands heart Foundation			
Comments	Total age data (n = 4497) doesn't add up to sample size Good paper – following review of the paper with the CASP tool. Shows benefits of cascade testing. Once a patient diagnosed with FH was identified, they were expected to gather as many family members as possible for testing, therefore used both direct and indirect cascade testing. Probably would need more specific details on the average number of family members patients with FH identified though.			

Umans-Eckenhausen 2002

Bibliographic reference	Umans-Eckenhausen 2002
Study type	Cohort
Aim	To assess the effect of different LDL receptor gene mutations on plasma lipoproteins and risk of CVD, after adjusting for familial risk factors
Patient characteristics	Relatives of index cases
Number of patients	1695 relatives of 66 index cases
Index test	LDL receptor gene mutation. Selection was based solely on the mendelian inheritance pattern of the LDL receptor mutations and not on referral type.
Reference standard (or Gold standard)	N/A

Bibliographic reference	Umans-Eckenhausen 2002
Time between testing & treatment	N/A
Length of follow-up	N/A
Location	Amsterdam, Netherlands
Results	N=608 carriers of LDL gene mutation. N=399 were not receiving medication. N=1087 non-carriers, 1048 not receiving medication

		Null Alleles		Other Alleles		Unaffected relatives	
N (total)		124		484		1087	
Mean age, y±SEM		34.8±1.6		36.8±0.9		40.7_0.6	
Age range, y		16-80		16-84		16–96	
Sex, male/female		61/63		233/251		511/576	
Risk Factors, no. (%±SEM)							
Hypertension		9 (7±2%)		17 (4±1%)		62 (6_0%)	
Diabetes, type 2		0 (0±0%)		2 (0±0%)		26 (2_1%)	
Former smokers		29 (23±4%)		77 (16±2%)*		197 (18_1%)	
Current smokers		32 (26±4%)		93 (19±2%)**		284 (26_1%)	
N (untreated)	26 (f)		28 (m)	178 (f)	167 (m)	559 (f)	495 (M)
Total Cholesterol, mg/dL	328 (67)		291 (48)	289 (63)	277 (52)	199 (45)	213 (58)
LDL Cholesterol, mg/dL	258 (59)		229 (44)	217 (59)	211 (49)	134 (40)	137 (40)
HDL cholesterol, mg/dL	39 (8)		37 (10)	45 (14)	37 (12)	49 (14)	41 (13)
Triglycerides, mg/dL	153 (78)		128 (73)	126 (79)	135 (86)	103 (89)	168 (115)

Bibliographic reference	Umans-Eckenhausen 2002
	Lipoprotein values are mean values (_SD). *In comparison with the other two groups, *P*_0.2; in comparison with the null alleles group, *P*_0.07. **Significantly lower than in the other two groups (*P*_0.03).
Source of funding	This work was supported by grants from the Dutch Ministry of Public Health, Welfare, and Sport, the Health Care Insurance Council, and the Netherlands Heart Foundation.
Comments	To avoid ascertainment bias, index cases were excluded from all analyses, since a proportion could have been referred based on the onset of CVD and this would lead to overestimation of the risk from FH. On the other hand, index cases were selected on being alive, which could also introduce a selection bias leading to underestimation of the risk from the disorder. Individuals receiving any form of cholesterol-lowering medication were excluded from analyses of the lipid and lipoprotein parameters. CASP tool – good paper, scored well with tool.

Van Maarle 2002

Bibliographic reference	Van Maarle 2002
Study type	Prospective cohort
Aim	To assess preventative care and the short term clinical outcome in people testing positive for FH as a proxy for expected long term level of coronary artery disease
Patient characteristics	N=677. Aged 18 and over Gave consent to genetic testing and the study A positive FH test result
Number of patients	677 people screened as part of the programme -215 tested positive for FH
Index test	Genetic screening
Reference standard (or Gold standard)	Key recommendations of the Dutch guidelines on hypercholesterolaemia and quality of clinical outcome by achieved cholesterol level, body mass index, and smoking status
Time between testing & treatment:	Not detailed
Length of follow-up	18 months (questionnaires completed at screening, 7 months and 18 months)
Location	Netherlands
Results	N=215 tested positive for FH. N=166 responded to questionnaire

Bibliographic reference	Van Maarle 2002
	Lost to follow up – differed in only 1 characteristic – use of statin (57% vs 39% [<0.05) Newly identified cases n=41 Confirmed cases (known to have FH at screening) n= 125 Proportion of people referred for treatment (drug/statin/ diet)

	Newly identified (n=41)		Confirmed cases (n=125)	
	At screening	Follow up	At screening	Follow up
Use of drugs	0	14 (34%)	99 (79%)	113 (90%)
Statins	0	14	95 (76%)	102 (82%)
Diet	5 (12%)	19 (46%)	87 (70%)	94 (75%

Source of funding	Health Research and Development Council of the Netherlands (grant number 282751).
Comments	QA by use of the CASP tool: Focussed aim and recruited in an appropriate way, but not sure how any biases or confounding factors were managed as this isn't detailed in the paper. Don't think the follow up time was long enough for the aims. Think the results can be applied to the local population to a level as FH is a genetic condition.

Vergotine 2001

Bibliographic reference	Vergotine 2001
Study type	Prospective
Aim	DNA diagnosis of FH evaluated against biochemical diagnosis used to identify subjects with FH
Patient characteristics	Hypercholesterolaemics referred for a molecular diagnosis of FH. Evaluation of biochemical vs DNA diagnosis performed in families with Afrikaner foundation mutations D206E, V408M, D154N. Index patients were selected on the basis of elevated TC levels, genotype/ phenotype correlation studies were only performed on family members recruited through tracing of defective genes in the pedigree. Follow up mutation screening performed/ extended in families where FH related mutation had been identified in the index case. Index cases without known mutations subject to extensive mutation screening followed by mutation screening in relevant at-risk relatives. In these index patients, pretreatment TC levels had to be at least equal to 90th percentile for age and gender, with normal triglyceride levels. The FH study participants had to either have clinical features of FH or a family history of CHD.
Number of patients	379 index cases and 790 at risk relatives
Index test	Genetic testing

Bibliographic reference	Vergotine 2001
Reference standard (or Gold standard)	MEDPED
Time between testing & treatment	N/A
Length of follow-up	N/A
Location	South Africa
Results	65 mutations identified in 379 index cases 338/790 inherited disease related LDLR gene mutation Reported data on 443 at-risk family members (screened for 1 of 3 Afrikaner founder mutations) NPV: 89.3.% PPV: 81.9% FH diagnosis according to TC values (using 80th percentile values) Sensitivity: 89.3% Specificity: 81.9%

Mutation	No. relatives	>95th percentile (%)	>80th percentile (%)
D206E	93	61 (66)	82 (88)
V408M	27	20 (74)	23 (85)
D154N	30	25 (83)	29 (97)
No mutation	293	12 (4)	53 (18)
Total	443	118	187

Source of funding	University of Stellenbosch, Tygerberg hospital, South African Medical Research Council, grant from Merck.
Comments	CASP appraisal: Unclear whether mutations identified are applicable to wider population.

G.1.2 Primary care

Bell 2014b

Bibliographic reference	Bell 2014b
Study type	Retrospective review & prospective case finding

<table>
<tr><th>Bibliographic reference</th><td>Bell 2014b</td></tr>
<tr><th>Aim</th><td>Whether individuals with FH can be identified in primary care (agreement between primary care and specialist)</td></tr>
<tr><th>Patient characteristics</th><td>People at risk identified by laboratory reports of high LDL-C concentration, or by using informatics tool to search the primary care database.</td></tr>
<tr><th>Number of patients</th><td>153,n=80 male, median age 54 (9) yrs, TC 7.5 mmol/L, n=93 on statin therapy.</td></tr>
<tr><th>Index test</th><td>DLCNS assessment by primary care (one of 3 nurses and 1 of 2 GPs) & genetic testing
Nurse interviewed and examined all individuals at risk and collect data required to calculate DLNCS.
GP would review data and calculate DLNCS.
Clinical FH defined as probable or definite FH using DLCNC categories.</td></tr>
<tr><th>Reference standard (or Gold standard)</th><td>Assessment by specialist:
Lipid specialist calculated DLCNS on de-identified data. Lipid specialist blinded to GP’s DLNCS.
If patient on lipid-lowering treatment, 30% added to LDL-c whilst on lipid lowering therapy.
Lipid specialist subsequently reviewed 30 individuals with DLNCS >4 as assessed by lipid specialist with primary care data, in telehealth clinic and determined their likelihood of FH using information obtained during this consultation. Lipid specialist blinded to all previous DLNCS and FH genetic testing until they had calculated the DLNCS for the telehealth consultation.</td></tr>
<tr><th>Time between testing & treatment</th><td>N/A</td></tr>
<tr><th>Length of follow-up</th><td>N/A</td></tr>
<tr><th>Location</th><td>Australia</td></tr>
<tr><th>Results</th><td>Diagnostic yield
Specialist: 45 individuals with clinical FH (probable or definite)
GP assessed 39/45 of these correctly.
GPs had specificity of 60% and sensitivity of 80% compared with specialist diagnosis in telehealth review.
<table>
<tr><td>Likelihood of FH as assessed by GPs</td><td colspan="5">Likelihood of FH as assessed by the specialist</td></tr>
<tr><td></td><td>Unlikely (0-2)</td><td>Possible (3-5)</td><td>Probable (6-8)</td><td>Definite (>8)</td><td>Total</td></tr>
<tr><td>Unlikely (0-2)</td><td>32</td><td>2</td><td>0</td><td>0</td><td>34</td></tr>
<tr><td>Possible (3-5)</td><td>1</td><td>66</td><td>13</td><td>0</td><td>80</td></tr>
<tr><td>Probable (6-8)</td><td>1</td><td>5</td><td>27</td><td>1</td><td>34</td></tr>
<tr><td>Definite (>8)</td><td>0</td><td>1</td><td>1</td><td>3</td><td>5</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Bell 2014b
	<table><tr><td>Total</td><td>34</td><td>74</td><td>41</td><td>4</td><td>153</td></tr></table> Genetic testing performed in 30 individuals assessed by specialist; 4 had disease causing mutations.
Source of funding	Sub study of research that received funding from Val Lishman Foundation and Royalties for Regions
Comments	CASP appraisal: Low quality (serious concerns about validity of results and unsure whether results could be applied locally). There was a lack of detail about the informatics tool and the search terms used within it. Lack of details as to what concentration of DL-C was considered elevated. No detail about the population of the GP database.

Gray 2008

Bibliographic reference	Gray 2008
Study type	Case identification through search of primary care database (electronic and manual search)
Aim	To assess the utility of combined computer and notes-based searches in identifying index cases of FH in primary care, and to uncover the degree of case overlap with secondary care.
Patient characteristics	• 108 (0.89%) patients had ischemic heart disease (IHD), including 35 with early onset IHD • 106 (0.87%) had a lipid diagnosis • 290 (2.4%) were receiving a statin • 1596 (13.2%) patients had a cholesterol test recorded on the computer • Young age profile mentioned in discussion but mean age not reported??
Number of patients	12,100 patients in a south London medical practice.
Index test	Dutch criteria used Computer searches for: IHD, lipids, statin, cholesterol >7.00 mmol/L (n=402 identified) Computer record and notes searched – data entered onto spreadsheet and Dutch core calculated for each patient. Specialist review by lipidologist and GP, n=169 excluded.
Reference standard (or Gold standard)	N/A
Time between testing & treatment	n/a
Length of follow-up	n/a
Location	South London GP practice.
Results	Dutch score >8 (definite)= 12 Dutch score 5-8 (probable)= 8

Bibliographic reference	Gray 2008
	3-5 (possible) = 216 (47 requiring future face-face interview) <3 (unlikely)= 166 **Early-onset IHD** TP = 9 FP = 26 FN = 11 TN = 12054 Sensitivity = 45.0 (25.8, 65.8) Specificity = 99.8 (99.7, 99.2) **Cholesterol > 7.5** TP = 17 FP = 108 FN = 1 TN = 11974 Sensitivity = 94.4 (74.2, 99.0) Specificity = 99.1 (98.9, 99.3) **Cholesterol > 7.0** TP = 20 FP = 181 FN = 0 TN = 11899 Sensitivity = 100 (83.9, 100.0) Specificity = 98.5 (98.3, 98.7)
Source of funding	Not reported
Comments	• In 30 cases, a higher cholesterol reading was recorded in the paper notes than on the computer records suggesting that computer records have not captured all the available information CASP appraisal: (Low quality due to concerns about validity of results). No DNA testing was undertaken to confirm FH, therefore DLCN diagnosis not verified. Computer searches constructed using read codes for IHD, lipid disorders, prescription for statins and cholesterol >7.0mol/L.

Green 2016

Bibliographic reference	Green 2016
Study type	Prospective: primary care database audit, followed by nurse-led cascade testing.
Aim	To improve detection of FH by identifying people with raised cholesterol concentrations.
Patient characteristics	Patients who visited their GP who were identified as being at potential risk of FH via the audit tool.
Number of patients	Approximately 290,000 from 56 general practices in Medway CCG.
Index test	Two-stage study: 1. Audit undertaken using search terms for TC >7.5 mmol/L in adults or >4.0 mmol/L in children <16 years or LDL-C >4.9mmol/L in adults or >4.0mmol/L in children, for further assessment. Over the next two years, electronic prompts appeared when the patient attended the practice to enhance GP decision making on FH diagnosis. 2. Nurse reviewed audit list of "at risk and unscreened" to identify any missing parameters. Once parameters collated, DLCN score calculated.
Reference standard (or Gold standard)	Simon Broome criteria
Time between testing & treatment	Not detailed
Length of follow-up	2 years (2011-2014) for audit, 9 months nurse led clinics
Location	Medway CCG, UK
Results	**Baseline (diagnosed using SB criteria):** FH: 331/262,030 Probable FH: N/A Possible FH: 12/ 262,030 **2 year audit (diagnosed using SB criteria):** FH: 354/ 199,346 Probable FH: n/a Possible FH: 88/ 199,346 **Nurse advisor programme (diagnosed using DLNC or SB criteria):** FH: 546/281,655 Probable FH: 83/ 281,655 Possible FH: 147/ 281,655
Source of funding	The NHS Medway FH Audit tool was supported from Medway CCG annual budget.

Bibliographic reference	Green 2016
Comments	Also reports at risk and unscreened – T/c >7.5mmol/L and/ or LDL-C>4.9 mmol/L and had not been assessed using SB criteria. 1164/199,346 at 2 year audit, 398/281,655 for nurse advisor programme. Paper not clear to follow. Unsure of the patient pathways following identification from the audit tool. GP practices were already using tool before the study, so were familiar with it. This could lead to some bias. Would have been better for GPs who were naïve to the tool to be tested. Not sure how this could be applied to a wider population – as it has funding implications. CASP appraisal: (Moderate due to concerns about validity of results) No DNA testing was undertaken to to confirm FH. People identified throught the audit+ tool only received a diagnosis of possible FH according to SB criteria, o further verification of the diagnosis was described. As a whole, the paper and figures reported within it were unclear and difficult to follow.

Kirke 2015

Bibliographic reference	Kirke 2015
Study type	Prospective
Aim	To compare three methods of case detection for identifying FH
Patient characteristics	Workplace screening: workforce of a large mineral processing operation. Workers offered short, 5 question questionnaire on CAD risk, administered as part of their annual health assessment. Participation voluntary. Respondants identifying 2 or more positive responses for CAD were contacted by a research nurse and offered a primary care assessment. GP database: screening of electronic records of 2 private general practices using data extraction software (Canning Tool). Criteria were: age 18-70 yrs, history of cardiac event <60 yrs, any CAD, diagnosis of lipid disorder, TC >7.5mmol/L, LDL >4.0mmol/L or prescription for statins. Unclear what contact patients had when informed if high risk. Pathology laboratory: involved 3 pathology laboratory providers, performed data extraction of records of all patients aged 18-60 yrs with TC >7.5mmol/L or LDLC >4.5mmol/L over previous 5 years from south west Australia postcodes. Pathology laboratories contacted patients by mail and they were recruited when they contacted the research office for a primary care assessment. All participants at risk of CAD or elevated cholesterol invited to participate in 30 minute face-face assessment by a trained nurse to screen for FH: assessment included medical and family history and calculation of dutch lipid network score (DLCNCS). Pretreatement score calculated if taking cholesterol lowering treatment by adding 30%

Bibliographic reference	Kirke 2015
	to cholesterol value. People with DLCN score >5 high risk and were invited to further follow up at specialist lipid clinic via referral from their GP; patients with >5 offered DNA testing that required informed consent. DNA testing included APOB, LDLR and PCSK9. Children and adolescents not included in risk assessment.
Number of patients	94379 patients recruited from workplace (primary care), GP practice (primary care) or pathology laboratory database (secondary care) Primary care: 42179 Secondary care: 52200
Index test	Dutch lipid criteria
Reference standard (or Gold standard)	DNA diagnosis: LDLR, APOB and PCSK9
Time between testing & treatment	N/A
Length of follow-up	N/A
Location	Australia
Results	94,379 patients/ questionnaires/ records screened for increased CV risk; Path lab: 52200 patient results Workplace assessment: 1079 risk questionnaires GP database: 41100 patient records 7279 participants with increased CV risk invited for clinical assessment of FH risk (n= 5963 declined invitation, n=1230 low risk of FH) Path lab: 4517 Workplace assessment: 268 GP database: 2494 86 participants high risk FH offered referral to specialist (Dutch lipid score >5): (27 declined referral or failed to respond) Path lab: 51 Workplace assessment: 3 GP database: 32

Bibliographic reference	Kirke 2015
	59 reviewed by lipid specialist and DNA tested: Path lab: 30 Workplace assessment: 3 GP database: 26 11 DNA positive, n=48 DNA negative Path lab: 8 Workplace assessment: 0 GP database: 3 Uptake of specialist review (people at high risk): Pathology lab: 597/4517= 13% Workplace: 30/268= 22% GP: 659/2494= 26% Uptake of DNA testing= 69% Path lab:30/51= 58.8% Workplace: 3/3= 100% GP: 26/31= 83.9%
Source of funding	Val Lishman Health Research Foundation, Royalties for regions and lottery west funding
Comments	DNA analysis – complete screen, no measurement bias. Selection bias for workplace assessment group as people volunteered to take part in assessment of risk. Uptake rates differed between groups, may lead to bias in reporting. Unclear how GP group contacted if they were at high risk of FH (1st stage of screening), no details provided in paper. CASP appraisal: (Low qulaitydue to concerns about validity of results) Recruitement of workplace portion of participants was voluntary, therefore susceptible to selection bias.

Norsworthy 2014

Bibliographic reference	Norsworthy 2014
Study type	Generation Scotland: Scottish Family Health study (pathology database)

Bibliographic reference	Norsworthy 2014
Aim	Targeted use of next generation sequencing as a potential route to diagnosis of FH in primary care population subset selected for hypercholesterolaemia. Cascade testing using molecular diagnostics.
Patient characteristics	Biological samples were obtained from the 'Generation Scotland: Scottish family Health study (GS:SFHS). Samples collected were from patients who were likely to have FH, based on previously reported population total cholesterol data in FH. Age and BMI thresholds were also used to reduce the inclusion of age and obesity related cases of hyperlipidaemia.
Number of patients	617 (selected on basis of total cholesterol data).
Index test	Patients were selected from the cohort using searches for TC, age and BMI cut-offs, tered the "High cholesterol group" (TC >8.5 mmol/L, TC 8-8.4mmol/L age <50 yrs, TC 8-8.4 mmol/L / age >50/ bmi <25, TC 7-7.9 mmol/L/ age <40) A cholesterol therapy group was selected (moderately high cholesterol despite lipid lowering therapy), and a control group.
Reference standard (or Gold standard)	Genetic testing for FH.
Time between testing & treatment	N/A
Length of follow-up	N/A
Location	Scotland
Results	**Diagnostic yield** **FH causing mutations identified through screening in :** 4/193 (2.1%) of subjects in high cholesterol group 5/232 (2.2%) in cholesterol therapy group 0/192 in normocholesterolaemic group **Cascade testing:** DNA available for cascade testing in relatives of 6/9 (66%) index cases identified. 12 available first degree relatives (FDRs) 5 molecular diagnoses of FH were made.
Source of funding	Generation Scotland has received core funding from the Chief Scientist Office of the Scottish Government Health Directorates CZD/16/6 and the Scottish Funding Council HR03006. We also acknowledge funding from the MRC Clinical Sciences Centre and the British Heart Foundation to TJA, from a Wellcome Trust Clinical Training Fellowship to ERAT, and from the NIHR-funded Imperial Biomedical Research Centre to TJA.
Comments	Data for LDL-C not reported in this study

Bibliographic reference	Norsworthy 2014
	CASP appraisal: (Very low quality due to concerns about validity of results, and whether the results will help locally) This was a database study, not primary research. The population of the study was older (35-65 years) at recruitement. LDL-C concentration not routinely collected,therefore recruitment on basis of TC and age only, which does not reflect how a person with FH would be identified in the real world as it ay identify a broader population than those truly at risk of FH.

Qureshi 2016

Bibliographic reference	Qureshi 2016
Study type	Prospective (feasibility study)
Aim	To assess the feasibility of improving identification of FH in primary care, and of collecting outcome measures to inform a future trial.
Patient characteristics	6 GP practices in central England. People with TC >7.5mmol/L and aged >18 years
Number of patients	N=831
Index test	Simon Broome
Reference standard (or Gold standard)	N/A
Time between testing & treatment	N/A
Length of follow-up	17 months duration
Location	UK
Results	831 eligible patients with TC >7.5 mmol/L. N=127 consented and recruited to study (via mail-out and opportunistic study packs) N=125 eligible for assessment N=32 with possible FH (Simon Broome) N=14 patients seen by GP, n=9 referred by GP N=7 seen by specialist Referral outcomes: N=2 definite FH N=5 confirmed possible FH
Source of funding	NIHR school of primary care research
Comments	CASP appraisal: (Low quality due to concerns about validity of results).

Bibliographic reference	Qureshi 2016
	This was a small study, the primary focus of which was not identifying uptake rate; rather it was the influence of an educational intervention for healthcare professionals on the identification of people with FH. There was no genetic confirmation of diagnosis ad there was a very low uptake rate of the intervention.

Troeung 2016

Bibliographic reference	Troeung 2016
Study type	Retrospective review of medical records
Aim	To evaluate the performance of a new electronic screening tool (TARB-Ex) in detecting general practice patients at potential risk of familial hypercholesterolaemia (FH).
Patient characteristics	Patients from large General practice • 53.3% female • Mean age 43.5±24.6 years • 1126 (30.4%) had at least one recorded LDL-C measurement • 39 patients on statin treatment at the time of highest LDL-C measurement and required cholesterol correction • 35 patients had a recorded history of premature cardiovascular disease and 2 had premature ischemic heart disease
Number of patients	3708 for screening N=360 with high lipid concentration identified.
Index test	Dutch Lipid Network Criteria >5 using TARB-Ex (electronic medical records search). Searched for active patients with 3 or more visits within the last 3 years, TC ≥7.0 mmol/L or LDL-C ≥4.0 mmol/L, family history using drop down and free text (a dictionary of terms was created to account for variation).
Reference standard (or Gold standard)	GP review using DLNC
Time between testing & treatment	N/A
Length of follow-up	Clinical follow up: patients considered at high risk of FH were recalled for clinical assessment with the GP and lipid specialist team – length of follow-up unclear
Location	Australia
Results	**Electronic screening:** Possible FH: (DLNCS 3-5): 76 Probable: (DLNCS 6-8): 3 Definite (DLNCS >9): 0

Bibliographic reference	Troeung 2016
	Total at risk (DCLNS ≥ 5): n = 32 (1 patient had existing diagnosis of FH) **Manual review:** GP manually reviewed n=360 with high lipid concentration Identified n=22 at risk of FH (DLNCS >5) **GP review of TARB-X and manual records:** Identified 10 people at high risk of FH. 22 excluded due to overcorrection of LDL-C concentration. 3/10 unable to attend 6/7 diagnosed with phenotypic FH on clinical examination 1 referred for genetic testing for FH. Agreement between 2 methods: Sensitivity: 95.5% Specificity: 96.7% PPV: 65.6% NPV: 99.7%
Source of funding	Supported through the Australian Government's Collaborative Research Networks (CRN) programme
Comments	• Statin strength data were not extractable in the electronic medical records and so the lowest adjustment factor for each medication was applied as a conservative strategy CASP appraisal: (Moderate quality due to concerns about validity of results). There was no genetic confirmation of the diagnosis of FH and details about family history missing for 65.2% of patients

G.1.3 Secondary care

Bates 2008

Bibliographic reference	Bates 2008
Study type	Retrospective
Aim	To investigate the prevalence of FH in patients of a younger age group presenting to cardiology service.

Bibliographic reference	Bates 2008
Patient characteristics	Cardiac patients presenting to cardiology department with cardiac type chest pain, or diagnostic coronary angiography, men <55 yrs, women <60 yrs; Mean age 49 (SD 7.2); 65% men; 69% Caucasian; 26% diabetic; 55% hypertensive; 69% current or ex-smokers; 43% taking statins on admission; TC 5.3 mmol/L; LDL-C 3.2 mmol/L (sd 1.1 mmol/L);
Number of patients	509/917 available were selected randomly for audit 334 patients met inclusion criteria
Index test	Dutch Lipid Network Criteria used to assess diagnosis of FH. Classed as indeterminate if insufficient information available to assess FH status.
Reference standard (or Gold standard)	N/A
Time between testing & treatment	N/A
Length of follow-up	N/A
Location	Australia
Results	(% reported only, n calculated by analyst) Definite/ probable:1.2%, n=4 Possible: 30.5%, n= 102 Unlikely: 27.8%, n=93 Indeterminate: 40.4%, n= 135
Source of funding	Pfizer
Comments	CASP appraisal: No issues.

Bell 2012

Bibliographic reference	Bell 2012
Study type	Case series
Aim	To determine the ability of a laboratory to screen for individuals with potential FH
Patient characteristics	Serum LDL concentrations reviewed over a 1 year period (2010-2011) in western Australia. All serum cholesterol requests were included, no exclusion criteria.
Number of patients	• 99,467 serum LDL cholesterol results from 84,823 people. • GPs requested 91.8%, cardiologist requested 3.2%. Other 5% requested by other specialists.

<table>
<tr><th>Bibliographic reference</th><th>Bell 2012</th></tr>
<tr><td></td><td>

51.2% of LDL cholesterol measurements performed in women (mean age 56 ±15 years); 48.8% in men (mean age 56+15 years)
Median and mean serum LDL-cholesterol concentrations were 3.0 and 3.1mmol/l respectively

</td></tr>
<tr><td>Index test</td><td>Comparison of MED-PED, dutch lipid network criteria and Simon Broome criteria.</td></tr>
<tr><td>Reference standard (or Gold standard)</td><td>N/A</td></tr>
<tr><td>Time between testing & treatment</td><td>Not reported</td></tr>
<tr><td>Length of follow-up</td><td>1 year period</td></tr>
<tr><td>Location</td><td>Australia</td></tr>
<tr><td>Results</td><td>
Medped:
<table>
<tr><td>criteria</td><td>People meeting criteria/ number of people in age category</td></tr>
<tr><td>Age <20 yrs, LDL >5.1 mmol/L</td><td>6/748</td></tr>
<tr><td>Age 20-29 yrs, LDL cholesterol >5.6 mmol/L</td><td>19/2980</td></tr>
<tr><td>Age 30-39 yrs, LDL cholesterol >6.5 mmol/L</td><td>33/7169</td></tr>
<tr><td>Age >40 yrs, LDL >6.7 mmol/L</td><td>118/73926</td></tr>
</table>

Simon Broome (serum LDL-C cutoff of >4.9 mmol/L in people aged >16 yrs.
3124/84823 (prevalence 1:27)

Dutch lipid network criteria:
<table>
<tr><td>Categories (LDL-C concentration, mmol/L)</td><td>Number of people (n=84823) (prevalence)</td></tr>
<tr><td>4.0-4.9</td><td>11030 (1:8)</td></tr>
<tr><td>5.0-6.4</td><td>2911 (1:29)</td></tr>
<tr><td>6.5-8.4</td><td>198 (1:428)</td></tr>
<tr><td>>8.5</td><td>15 (1:5655)</td></tr>
</table>

Potential FH based on non-age adjusted LDL-cholesterol cut offs:
<table>
<tr><td>LDL-C (mmol/L)</td><td>Number of people (prevalence)</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Bell 2012	
	>8.5	15 (1:5655)
	>8.0	23 (1:3688)
	>7.5	48 (1:1767)
	>7.0	90 (1:942)
	>6.5	213 (1:398)
	>6.0	472 (1:180)
	>5.5	1227 (1:69)
	>5.0	3124 (1:27)
	>4.5	6879 (1:12)
	>4.0	14154 (1:6)
Source of funding	None	
Comments	• No specialist review to confirm whether individuals had confirmed FH	

Bell 2014

Bibliographic reference	Bell 2014			
Study type	Case-control			
Aim	To determine whether a phone call from a chemical pathologist to requesting GP of individuals at high risk of FH increases specialist referral and detection of FH.			
Patient characteristics	People with raised cholesterol (>6.5mmol/L)l identified from community laboratory.			
	Characteristics	Controls	Cases	Significance
	N	96	100	
	Female (n)	68	57	0.05
	Age (yr), meand (SD)	53.7 (10.7)	49.3 (12.4)	0.009
	LDL-C (mmol/L)	7.1 (0.8)	7.1 (0.7)	1.0
	Referred to specialist, n	4 (4)	27 (27)	<0.0001
	Clinical (Probable or definite) FH, n (% of clinically assessed)	4 (4)	18 (18)	0.003
	Probable FH, n (% of clinically assessed)	2 (50%)	6 (24%)	

Bibliographic reference	Bell 2014			
	Definite FH, n (% of clinically assessed)	2 (50%)	12 (48%)	0.01
	Mutation identified, n (% of genetically tested)	2 (50%)	7 (30%)	
Number of patients	196 (100 cases, 96 controls)			
Index test	Cases received laboratory report comments and the GP received a telephone call from the chemical pathologist to highlight patient's risk of FH and suggest specialist referral.			
Reference standard (or Gold standard)	Control GPs were not phoned.			
Time between testing & treatment	N/A			
Length of follow-up	12 months			
Location	Australia			
Results	**Cases:** 27 referred to specialist clinic (1 known to be mutation positive, 2 failed to attend appt) 25 underwent specialist review 18 diagnosed with FH (6 probable, 12 definite) Genetic testing performed in 23 people. 7 had identifiable FH causing mutations. **Controls:** 4 referred to specialist clinic, all 4 diagnosed with FH. 2 probable, 2 definite. Genetic testing performed on all 4; 2 clinically definite FH had identifiable FH causing mutations, 2 probable individuals did not. **Cascade screening (cases only):** Genotypic cascade screening in 12 family members from 4 mutation positive FH individuals in intervention group; 7 confirmed to carry mutation, 5 did not.			
Source of funding	None			
Comments	CASP appraisal: Cases and controls significantly different in age. No other concerns			

Besso 1999

Bibliographic reference	Besso 1999
Study type	Prospective cohort
Aim	To develop an immunoassay for detection of hypercholesterolaemia – specifically aimed at neonates with hyperlipidaemias
Patient characteristics	Newborn infants in the King's Healthcare catchment on the 6th or 7th postnatal day
Number of patients	9673 neonates screened for FH
Index test	Blood samples taken by heel prick on the 6th or 7th postnatal day after all routine screening had been completed. Immunoturbidimetric assay of apo A-1 and B
Reference standard (or Gold standard)	Immunoneph apoA-1 and apoB reference standards
Time between testing & treatment	No treatment offered
Length of follow-up	No follow up within the study. All families were referred to the vascular risk clinic for diagnosis and follow up.
Location	England
Results	189 infants recalled (APOB levels in top percentile of each batch, or apo A1-B ratio of <1) 82 individuals attended recall clinic 16 families (24 individuals) had abnormal lipid profiles 7 had lipid profiles consistent with FH (14 individuals)

Family		Total cholesterol (mmol/l)	TAG (mmol/l)	HDL (mmol/l)	LDL (mmol/l)	HDL/TC ratio
Reference range	Infants Adult females Adult males	3.0-5.0 3.4-5.9 3.5-6.4	0.4-1.3 0.4-1.7 0.6-2.9	0.9-1.9 0.9-2.0 0.7-1.7	1.7-4.6 1.8-4.2 2.0-4.6	- - -
1	Infant Mother	1.8 7.7	1.4 2.7	- -	- 5.3	- 0.8
2	Infant Mother Father	[2.1]a 5.5 7.7	- 1.2 2.2	- 1.4 1.2	- 3.6 5.5	- 0.34 0.18
3	Infant	3.7	1.2	1.1	2.1	0.42

Bibliographic reference	Besso 1999						
		Mother	8.3	0.8	1.5	6.4	0.22
	4	Infant	4.2	1.2	1.0	2.7	0.31
		Mother	7.0	1.9	1.5	4.6	0.27
		Father	5.5	0.6	1.4	3.8	0.34
	5	Infant	5.7	2.7	1.2	3.3	0.26
		Mother	4.8	2.8	0.6	2.9	0.14
		Father	6.5	2.2	0.9	4.5	0.16
	6	Infant	5.1	1.7	0.9	3.6	0.21
		Mother	4.1	0.5	1.3	2.6	0.46
		Father	3.6	0.8	0.8	2.4	0.29
	7	Infant	3.8	1.1	0.9	2.4	0.31
		Mother	4.7	0.7	1.7	2.7	0.57
		Father	7.4	1.6	1.4	5.3	0.23
	8	Infant	6.4	2.4	1.4	3.9	0.28
		Mother	5.7	0.8	1.9	3.4	0.50
		father	8.1	1.1	0.8	6.8	0.11
	9	Infant	4.2	3.8	1.0	1.5	0.31
		Mother	5.1	0.8	1.6	3.1	0.46
		Father	8.1	2.5	1.5	5.5	0.23
	10	Infant	5.1	2.4	1.2	2.8	0.31
		Mother	4.0	0.7	1.2	2.5	0.43
		Father	5.8	1.4	1.2	4.0	0.26
	11	Infant	4.1	1.4	1.3	2.2	0.46
		Mother	4.8	0.5	1.2	3.4	0.33
		Father	6.3	0.9	1.8	4.1	0.40
	12	Infant	5.5	1.2	-	-	-
		Mother	5.3	0.9	1.3	3.6	0.33
		Father	4.9	1.3	1.0	3.3	0.26
	13	Infant	[1.53][a]	-	-	-	-
		Mother	3.6	1.5	1.0	1.9	0.38
		Father	6.6	2.3	0.7	4.9	0.12

Bibliographic reference	Besso 1999

14	Infant Mother Father	[1.59][a] 9.7 4.2	- 3.2 1.6	- 1.3 1.0	- 6.9 2.5	- 0.15 0.31
15	Infant Mother	6.7 Known FH	1.0 -	1.1 -	5.1 -	0.2 -
16	Infant Mother Father	7.0 5.6 5.2	0.9 0.6 1.7	1.0 - -	5.6 - -	0.17 - -
a If total cholesterol level is unknown in infants, blood spot apoB is given in square brackets (reference range 0.2±0.5 g/l). Other reference ranges are from [14] and represent the 5th to 95th percentiles for age and gender.						

Source of funding	South Thames Regional Health Authority
Comments	CASP – nothing to note, good paper.

Chung 1999

Bibliographic reference	Chung 1999
Study type	Cohort
Aim	To identify cases of FH in Taiwan
Patient characteristics	Patients with hyperlipidaemia attending metabolic clinic.
Number of patients	11
Index test	Simon Broome criteria which identifies a definitive or possible diagnosis of FH. A medical, cardiocascular and family history were taken, along with plasma lipid profiles. The thickness of xanthomas in patients were measured by soft tissue ultrasonography.
Reference standard (or Gold standard)	Simon Broome criteria
Time between testing & treatment	All patients received treatment, but this was initiated prior to the commencement of the study.
Length of follow-up	No follow up
Location	Taiwan
Results	5 had definitive FH 6 possible FH

Bibliographic reference	Chung 1999

Diagnosis	Age	Gender	BP (mmHg)	PH of CHD or CVA	FH of CHD or CVA	Pre-treatment			Post-treatment	
						TC	LDL	TG	TC	LDL
						(mg/dl)			(mg/dl)	
Definitive Familial hypercholesterolemia	60	F	117/54	CVA	CVA	116	254	103	288	188
	62	F	173/74	-	-	326	248	173	321	258
	46	F	104/66	-	-	418	346	105	311	236
	76	M	141/54	-	-	368	278	81	295	206
	48	M	130/60	CHD	CHD	637	549	292	524	465
Possible Familial hypercholesterolemia	36	F	110/72	CVA	CHD	339	245	101	277	188
	42	F	115/48	-	CVA	360	302	57	229	173
	56	M	174/85	-	-	406	332	134	250	189
	49	F	110/78	-	-	406	317	96	389	315
	36	F	90/60	-	-	382	323	53	433	341
	51	F	-	-	-	335	242	63	278	181

Source of funding	Not detailed
Comments	Secondary causes of hypercholesterolaemia, including abnormal liver function, endocrine disorders renal disease, as well as other known forms of hyperlipidaemia were excluded. Small sample and so some results not generalizable. All patients recruited into the trial were being treated at a metabolic clinic already so sample biased. All were already receiving treatment for their hyperlipidaemia which may mean the results were not accurate of their true biochemical measurements.

Clarke 2013

Bibliographic reference	Clarke 2013
Study type	Retrospective review of new FH presentations from a university teaching hospital lipid clinic.
Aim	To determine utility of secondary stratification measures to improve ascertainment of index cases of FH
Patient characteristics	• 112 with identified FH mutations, 92 with no monogenic FH mutation • Genetic diagnosis obtained in 75% of TX-patients and 44% TX+ patients • Age: 55 ± 14 years • 47% male • LDL-C was 6.20 (2.24) mmol/l • 21% with established CHD
Number of patients	204 FH patients in lipid clinic registry, using Simon Broome criteria
Index test	Dutch criteria, lipoprotein A, history of CHD, family history CHD or TC, cholesterol concentrations.
Reference standard (or Gold standard)	Simon Broome criteria (for purposes of case-finding review: genetic testing was undertaken but was not the reference standard for case-finding).
Time between testing & treatment	Not reported
Length of follow-up	N/A
Location	UK
Results	See table below

Criteria	TP	TN	FP	FN	Sensitivity	Specificity
Simon Broome (+)	112	0	92	0	100 (96.7, 100)	0 (0, 4.0)
SB possible	65	0	92	47	58.0 (48.8, 66.8)	0 (0, 4.0)
Dutch score >5	78	59	33	34	69.6 (60.6, 77.4)	64.1 (53.9, 73.2)
Lp(a) >0.5g/L	37	49	41	73	33.6 (25.5, 42.9)	54.4 (44.2, 64.3)
Personal history CHD <60 yrs	26	81	11	86	23.2 (16.4, 31.8)	88.0 (79.8, 93.2)
Relative with CHD at <60 yrs	53	57	35	59	47.3 (38.3, 56.5)	62.0 (51.7, 71.2)
Relative with TC >7.5 mmol/L	17	74	18	95	15.2 (9.7, 23.0)	80.4 (71.2, 87.3)
LDL-C >8 mmol/L	26	89	3	86	23.2 (16.4, 31.8)	96.7 (90.8, 98.9)

Bibliographic reference	Clarke 2013						
	LDL-C >6.5 mmol/L	61	76	16	51	54.4 (45.2, 63.4)	82.6 (73.6, 89.0)
	LDL-C >5 mmol/L	92	31	61	20	82.1 (74.0, 88.1)	33.7 (24.9, 43.8)
	LDL-C >4mmol/L	100	20	72	12	89.3 (82.2, 93.8)	21.7 (31.2, 31.2)
	SB criteria + premature CHD					88	23
Source of funding	None						
Comments	• Retrospective • Cohort elected using Simon Broome criteria, genetic testing for LDLR, APOB and PCSK9 mutations was undertaken but it was not used asthe reference standard for case-finding of FH in this population. • Enough information was provided in the paper to assess the proportion of people diagnosed with FH with DLCN or SB who had genetic mutations in one of the three identified genes; therefore this paper could be included in the diagnostic review.						

De Backer 2015

Bibliographic reference	De Backer 2015
Study type	Cross sectional survey in 24 European countries; standardised interview, bioclinical examination and venous blood sampling
Aim	To estimate the prevalence of clinical heterozygous FH (HeFH) in a large group of patients with CHD who participated in the EUROASPIRE IV survey. Also, to compare the potential HeFH patients with the other patients with respect to different clinical characteristics and their management.
Patient characteristics	• Patients aged ≥18 and <80 years who had been hospitalised for a coronary event between 6 months and 3 years before the interview. • Mean age at interview, mean (SD): - Potential FH group: 58.2 (10.0) - Others: 64.8 (9.3) • 5335 men; 1709 women • Among all patients with potential FH, 55% were on high intensity statin
Number of patients	N=7044

Bibliographic reference	De Backer 2015
Index test	Adapted version of the Dutch Lipid Clinic Network Criteria – a score was given based on various criteria with the following definitions: - Unlikely FH – total score 0-2 - Possible FH-total score 3-5 - Probable FH – total score 6-8 - Definite FH – total score >8
Reference standard (or Gold standard)	N/A
Time between testing & treatment	Not reported
Length of follow-up	N/A
Location	Various – 24 European countries
Results	<table><tr><td>Category</td><td>N</td><td colspan="5">FH classification</td></tr><tr><td></td><td></td><td>Unlikely</td><td>Possible</td><td>Probable</td><td>Definite</td><td>potential</td></tr><tr><td>All</td><td>7044</td><td>4234</td><td>2223</td><td>510</td><td>77</td><td>587</td></tr><tr><td>Age <60 yrs</td><td>2212</td><td>719</td><td>1152</td><td>304</td><td>37</td><td>341</td></tr></table>
Source of funding	Survey was supported through unrestricted research grants to the European Society of Cardiology from Amgen, AstraZeneca, Bristol-Myers Squibb and AstraZeneca, F.Hoffman-La Roche, GlaxoSmithKline and Merck Sharp and Dohme.
Comments	None

Futema 2013

Bibliographic reference	Futema 2013
Study type	Cross sectional
Aim	To determine frequency and spectrum of mutations causing FH in patients attending a single UK specialist hospital lipid clinic in Oxford and to identify characteristics contributing to a high mutation detection rate.
Patient characteristics	All patients Caucasian, aged over 18 years, diagnosed with either definite or possible FH using Simon Broome criteria, or as having unclassified hypercholesterolaemia (UH) (defined as total cholesterol and/ or LDL-C above the SB criteria cut off (>7.5mmol/L or >4.9mmol/L respectively, but with no family history of early CHD or no family history that could be elicited). 52% (n=150) possible FH; 23% (n=65) definite FH; 26% (n=74) UH. No difference between age and male: female ratio between the 3 groups.

<table>
<tr><td>Bibliographic reference</td><td>Futema 2013</td></tr>
<tr><td></td><td>Mean pre-treatment cholesterol significantly different between groups: Definite had highest TC (9.79mmol/L) and LDL-C (6.93mmol/L) Possible and UH groups had similar pre-treatment TC and LDL-C levels. Highest pre-treatment Triglyceride levels observed in UH patients (2 mmol/L), significantly different between groups, but similar to possible FH group.</td></tr>
<tr><td>Number of patients</td><td>289 (272 probands)
Separate cohort of 409 FH patients classified using SB criteria, comparing to DLNC.</td></tr>
<tr><td>Index test</td><td>Genetic testing: APOB, LDLR, PCSK9 mutations
Simon Broome criteria
Dutch Lipid Network Criteria (DLNC)</td></tr>
<tr><td>Reference standard (or Gold standard)</td><td>Genetic testing</td></tr>
<tr><td>Time between testing & treatment</td><td>N/A</td></tr>
<tr><td>Length of follow-up</td><td>N/A</td></tr>
<tr><td>Location</td><td>UK</td></tr>
<tr><td>Results</td><td>Baseline characteristics of people classified with FH according to Simon Broome criteria
<table>
<tr><td>Mutation</td><td>Definite FH (SB)</td><td>Possible FH (SB)</td><td>Unclassified FH</td></tr>
<tr><td>+ve</td><td>44</td><td>38</td><td>10</td></tr>
<tr><td>-ve</td><td>16</td><td>104</td><td>60</td></tr>
</table>
Mutation found in 101 individuals (44/65 with definite FH; 38/150 with possible FH; 10/74 with UH)
<table>
<tr><td>DLCN</td><td>Number of patients</td><td>Mutation +ve (%)</td><td>Mutation –ve</td><td>DFH (SB) (%)</td><td>No FH (SB crit)</td></tr>
<tr><td><3</td><td>13</td><td>3 (23)</td><td>10</td><td>2 (15)</td><td>11</td></tr>
<tr><td>3-5</td><td>69</td><td>19 (28)</td><td>50</td><td>9 (13)</td><td>60</td></tr>
<tr><td>6-8</td><td>49</td><td>19 (39)</td><td>30</td><td>8 (16)</td><td>41</td></tr>
<tr><td>>8</td><td>89</td><td>48 (54)</td><td>41</td><td>45 (51)</td><td>44</td></tr>
<tr><td>Total</td><td>220</td><td>89</td><td>131</td><td>64</td><td>156</td></tr>
</table></td></tr>
<tr><td>Source of funding</td><td>NIHR paid for genetic testing</td></tr>
<tr><td>Comments</td><td>CASP critical appraisal:</td></tr>
</table>

Bibliographic reference	Futema 2013
	No concerns, appropriate genetic testing,

Haralambos 2015

Bibliographic reference	Haralambos 2015
Study type	Prospective cohort
Aim	To assess an FH scoring system based on modified DLCN criteria to guide genetic testing of index patients presenting with hypercholesterolaemia
Patient characteristics	1206 consecutive index patients who had been referred to lipid clinics inWales over the course of 24 months (between November 2010 and November 2012). The study group did not include relatives of index patients detected by cascade testing
Number of patients	1,206
Index test	Modified Dutch Lipid Clinic Network criteria (deducted points for high triglyceride concentrations)
Reference standard (or Gold standard)	Genetic testing of LDLR, APOB and PCSK9
Time between testing & treatment	N/A
Length of follow-up	N/A
Location	Lipid clinics, Wales
Methods and results	Patients with a score of 6 or greater were offered genetic testing. If a patient scored ess than 5 they would not routinely e offered genetic testing, but only if their clinicians considered that there were particular circumstances that may make FH more likely.(e,g, family history of CHD). 1206 patients scored N=547 score of ≥6. Of which, n=522 genotyped and 30 not genotyped. Variants (class 2-5) found in n=218 (41%) N=659 score of <6. Of which n=101 genotyped and 558 not genotyped. Variants found in n=13 (13%). 4 people had class 5 variants. LDLC correction factor applied on statins was applied 164/623 patients. N=173 class 5 variants identified. N=58 class 2-4 variants N=6 had a class 2 variant Diagnostic yield for genetic mutations at different score cut-offs:

Bibliographic reference	Haralambos 2015

Score cut off	Diagnostic yield
≥6	32%
≥7	40%
≥9	53%
≥11	66%
≥13	78%
≥15	85%

Cohort also scored for Simon Broome.
20% classified as SB definite. Mutation pick up rate of SBD was 60%
65% classified as possible Simon Broome. Mutation pick up rate for SBP 21%
Mutation pick up for those not meeting SB criteria was 14%

2x2 tables (n calculated by analyst, using% supplied in paper)

	N	TP	FP	FN	TN
Simon Broome definite	1206	145	96	190	775
Simon Broome possible and definite	1206	310	715	25	156
Modified DLCN possible and definite	623	171	351	4	97

Source of funding	Supported by Cardiff university and the Wales FH service
Comments	Only n=623 of people who had DLCN scoring genotyped. For SB cirteria, not reported how many had genetic test, therefore assumed all did.

Heath 2001

Bibliographic reference	Heath 2001
Study type	Retrospective
Aim	To describe the FH genetic testing service and diagnostic results over first 4 years of operation.
Patient characteristics	Patient diagnosed using Simon Broome criteria, adults and children
Number of patients	227 probands, 141 family members referred from lipid clinics and GPs People were referred if they had FH according to Simon Broome criteria.(definite or probable). Any child suspected of having FH but did not meet every criteria was still analysed for LDLR and APOB mutations.
Index test	Genetic testing
Reference standard (or Gold standard)	Genetic testing: from frozen whole blood or buccal samples; SSCP analysis. LDLR major rearrangements screened by analysing exons 3 5, 8, 14, 17 by universal primer. PCR. R3500Q and R3531C mutations screened by direct PCR. R3500W mutation only tested in patients of Asian background.
Time between testing & treatment	n/a
Length of follow-up	n/a
Location	UK
Results	Mutations designated as pathogenic identified in 76 probands; 67 in LDLR and 9 in APOB Adult detection rate: 28% (n=170) Paediatric : 53% (n=57) Significant difference p<0.01 Adults definite FH: (n=122), detection rate 32% Adults possible FH (n=48), detection rate 14% Significant p<0.01 Patients screened for APOB R3500Q mutation LDLR were screened by SSCP analysis
Source of funding	Not reported
Comments	States population included probands and relatives, only give number of mutations identified in probands, not relatives. Only analysed LDLR and APOB mutations, not PCSK9? Unclear why only one mutation assessed in Asian population only, no information about this provided elsewhere in literature

Hu 2013

Bibliographic reference	Hu 2013
Study type	Retrospective
Aim	To assess whether Chinese population had lower LDL concentration and prevalence of xanthomata in people with FH compared to Caucasian population.
Patient characteristics	<18 yrs: n= 43 Mean age 12.2 (SD 4.0),; xanthomata n=4/36 (11.1%); >18 yrs: n=209; mean age 41.9 (SD 13.4); xanthomata n=97/195 (49.7%); CHD n=18//200 (9.0%) From 1990-2000 132 families with a member who had TC >7.5mmol/L without secondary causes were screened.
Number of patients	446 (87 probands, 165 affected relatives)
Index test	Medped
Reference standard (or Gold standard)	Genetic testing: detection of mutations in the promotor and 18 coding exons of the LDLR using a double stranded DNA cycle sequencing kit.
Time between testing & treatment	n/a
Length of follow-up	n/a
Location	Hong Kong
Results	252 clinically diagnosed as He FH (87 probands and 165 relatives)/446 total people screened.
Source of funding	Not reported
Comments	Only searched for genetic mutations in LDLR gene.

Kirke 2015

Bibliographic reference	Kirke 2015
Study type	Prospective
Aim	To compare three methods of case detection for identifying FH
Patient characteristics	
Number of patients	94379 patients recruited from workplace (primary care), GP practice (primary care) or pathology laboratory database (secondary care)
Index test	Dutch lipid criteria
Reference standard (or Gold standard)	DNA diagnosis (LDLR, ApOB, PCSK9)

Bibliographic reference	Kirke 2015
Time between testing & treatment	n/a
Length of follow-up	n/a
Location	Australia
Results	94,379 patients/questionnaires/records screened for increased CV risk; Path lab: 52,200 patient results Workplace assessment: 1,079 risk questionnaires GP database: 41,100 patient records 7,279 participants with increased CV risk invited for clinical assessment of FH risk (n=5,963 declined invitation, n=1,230 low risk of FH) Path lab: 4,517 Workplace assessment: 268 GP database: 2,494 86 participants high risk FH offered referral to specialist (Dutch lipid score >5): (27 declined referral or failed to respond) Path lab: 51 Workplace assessment: 3 GP database: 32 59 reviewed by lipid specialist and DNA tested: Path lab: 30 Workplace assessment: 3 GP database: 26 11 DNA positive,(n=48 DNA negative) Path lab: 8 Workplace assessment: 0 GP database: 3
Source of funding	Val Lishman Health Research Foundation, Royalties for regions and lottery west funding
Comments	None

Klancar 2015

Bibliographic reference	Klancar 2015
Study type	Prospective
Aim	Genetic identification of FH from a cohort of children with elevated serum total cholesterol
Patient characteristics	Slovenian children born between 1989 and 2009, TC >6mmol/L or >5mmo/L and family history positive for premature cardiovascular complications. Age 7.3 (SD 3.1) years; cardiovascular complication rate –positive family history according to Simon Broome criteria in 33.1%
Number of patients	272
Index test	Serum total cholesterol (TC) level of more than 6 mmol/l (231.7 mg/dl) *without* family history of cardiovascular (CV) complications, or: Serum TC level of more than 5 mmol/l (193.1 mg/dl) *with* family history of CV complications
Reference standard (or Gold standard)	Genetic testing: next generation sequencing of APOB, LDLR, PCSK9, APOE.
Time between testing & treatment	N/A
Length of follow-up	N/A
Location	Slovenia
Results	FH= 155/272 (57%)
Source of funding	Not reported
Comments	Part of national screening program for hypercholesterolaemia in children.

Laurie 2004

Bibliographic reference	Laurie 2004
Study type	Letter to the editor
Aim	To discuss experience in implementing and maintaining a diagnostic screening program for low-density lipoprotein receptor and ApoB-100 gene mutations from both a clinical and laboratory perspective.
Patient characteristics	People with TC >8.0mmol/L selected for genetic screening
Number of patients	N=65
Index test	Genetic screening
Reference standard (or Gold standard)	n/a

Bibliographic reference	Laurie 2004
Time between testing & treatment	Not reported
Length of follow-up	Not reported
Location	New Zealand
Results	17% had LDLR mutation (n=33, calculated by analyst) ApoB-100 mutations in 1.6% (n=22, calculated by analyst) of patients screened since 1993 (n=1354)
Source of funding	Not reported
Comments	n/a

Medeiros 2010

Bibliographic reference	Medeiros 2010 / Bourbon 2007/ (data from Medeiros as more recent publication encompassing Bourbon 2007 data)
Study type	Case series
Aim	To identify the genetic cause of hypercholesterolaemia in individuals with a clinical diagnosis of Familial Hypercholesterolaemia
Patient characteristics	318 adults, 164 children
Number of patients	1340 blood samples from 482 index patients and 858 relatives, samples sent from secondary care.
Index test	Genetic testing (LDLR, APOB, PCSK9)
Reference standard (or Gold standard)	Modified Simon Broome
Time between testing & treatment	n/a
Length of follow-up	n/a
Location	Portugal
Results	From 482 index patients received, only 359 have their molecular study completed, results presented here. LDLR gene: 165 families, 80 mutations identified Screening of 443 individuals in 165 families – additional identification of 226 genetically diagnosed FH patients. APOB gene: Found in 3 unrelated index patients

Bibliographic reference	Medeiros 2010 / Bourbon 2007/ (data from Medeiros as more recent publication encompassing Bourbon 2007 data)
	PCSK9 gene:3 patients 52% patients it was not possible to identify a mutation in any of 3 genes analysed. Mutation found in 14% (8/59) of patients that did not fulfil the SB criteria Mutation identified in 45% children and 51% of adults studied (I.e. met SB and genetic criteria)
Source of funding	The following grants are acknowledge: “Clinical and molecu-lar characterization of Portuguese FH patients” Portuguese Society of Cardiology (2006–2009), “PIC/IC/83333/2007” Science and Tech-nology Foundation (2009-2011) and SFRH/BD/27990/2006 (AC Alves, PhD grant) Science and Technology Foundation
Comments	CASP: Numbers analysed: referred are unclear. Unclear whether includes probands and relatives.

Muir 2010

Bibliographic reference	Muir 2010
Study type	Retrospective
Aim	To identify the diagnostic and treatment rates for FH in New Zealand
Patient characteristics	People with a pre treatment cholesterol of >8 mmol/L, lipid stigmata or a strong family history of CVD were tested for mutations of LDLR gene; average of 147 per annnum.
Number of patients	588 people referred for mutation screening; 76 index cases identified; 353 relatives screened.
Index test	pre-treatment cholesterol _8.0 mmol/L, lipid stigmata or a strong family history of CVD
Reference standard (or Gold standard)	Genetic testing of LDLR gene.
Time between testing & treatment	N/A
Length of follow-up	N/A
Location	New Zealand
Results	Between 2004-2008, 588 people were identified from pathology laboratory database were DNA tested for FH if they had TC >8 mmol/L (pre-treatment); lipid stigmata or a strong family history of CVD. 76 index cases identified from path lab database (76/588) Cascade testing:

Bibliographic reference	Muir 2010
	Patients with an identified mutation referred to clinical nurse specialist at CDHB lipid clinic for cascade testing. 95 patients with a severe phenotype who met criteria for mutation analysis but did not have an identified mutation, were also referred. All index patients provided contact details for their relatives who were sent letters explaining FH, consent forms and laboratory request forms. 353 relatives screened. 159/353 (43.34%) positive familial LDLR mutation
Source of funding	None reported.
Comments	Not clear how many people were invited to cascade screening, unable to calculate uptake rate. Only one genetic mutation analysed? LDLR only? No follow up of patients with severe disease phenotype but no mutation, or children of index patients who had reached teenage years

Nanchen 2015

Bibliographic reference	Nanchen 2015
Study type	Retrospective multi-centre cohort study, secondary care database (Coronary)
Aim	To assess prevalence and management of clinical FH among patients with acute coronary syndrome (ACS)
Patient characteristics	• Patients with acute coronary syndrome • 1425 patients using lipid lowering drugs before hospitalisation

	Dutch Lipid Clinic Network			Simon Broome Register	
	Probable/definite FH (>5 points)	**Possible FH (3-5 points)**	**No FH**	**Possible FH**	**No FH**
Age in years, mean (SD)	49.5 (9.3)	52.4 (10)	64.8 (11.5)	51.6 (9.8)	63.8 (12.2)
Female, n(%)	18 (23.1)	172 (20.2)	818 (21.3)	62 (23.9)	946 (20.9)
Premature CHD, n(%)	70 (89.7)	684 (80.3)	697 (18.1)	203 (78.4)	1248 (27.6)

Bibliographic reference	Nanchen 2015					
	LDL-cholesterol in mmol/l, mean (SD)	6.6 (1.6)	4.3 (1.1)	3.2 (0.9)	5.8 (1.1)	3.3 (1.0)
	Statins, n(%)	31 (39.7)	199 (23.4)	1155 (30.0)	84 (32.4)	1301 (28.8)
Number of patients	4778 patients with ACS from multicentre cohort in Switzerland					
Index test	People diagnosed with ACS.					
Reference standard (or Gold standard)	Dutch Lipid Clinic Network (DLCN) Criteria – possible diagnosis with score 3-5, probable/definite diagnosis when score 6 or higher. Simon Broome criteria – requires both an elevated LDL-cholesterol ?4.9mmol/l (or total cholesterol >7.5mmol/l) along with a family/personal history of premature atherosclerosis					
Time between testing & treatment	Not reported					
Length of follow-up	Not reported					
Location	Switzerland					
Results	**Diagnostic yield** DLNC: Probable/ definite:78/4778 Possible: 852/4778 SB criteria: Possible:259/4778 Combined DLCN + SB: Probable/ definite: 77 (977 patients identified with either DLNC or SB in total)					
Source of funding	Supported by the Swiss National Science Foundation					
Comments	• Signs of lipid accumulation and genetic tests were not available, therefore a diagnosis of definite FH according to SB criteria could not be evaluated. • The study assessed the proportion of people with ACS assessed as having FH according to SB or DLCN criteria. The study did not report the agreement between SB and DLCN criteria in diagnosing FH. It was stated that this is available in supplementary onine material, however this could not be located. • Also compared prevalence of FH in people with ACS vs premature ACS: In premature ACS (N=1451)47.1% possible FH with DLNC, 4.8% probable/ definite; 14% possible FH with Simon Broome, 4.8% probable/ definite and 49.3% possible FH using combined definition					

Pang 2015

Bibliographic reference	Pang 2015
Study type	Prospective
Aim	To investigate point prevalence of FH in a coronary care unit among patients with early onset CAD.
Patient characteristics	Patients admitted with CAD at age <60 yrs (ACS, coronary revascularisation or angina)
Number of patients	175 patients recruited over a 2 12 week periods each in 2011 and 2013 of patients admitted to the CCU of the Royal Perth Hospital.
Index test	Modified Dutch Lipid Network Criteria and the prevalence of individuals with a family history of premature CAD, LDL cholesterol and the prevalence of meeting both the family history and LDL cholesterol assessment criteria.
Reference standard (or Gold standard)	Modified Dutch Lipid Network Criteria
Time between testing & treatment	No treatment given
Length of follow-up	2 periods of 12 weeks in 2011 & 2013
Location	Australia
Results	25 with FH 150 no FH

Prevalence of FH according to different criteria	With FH (n=25)	Without FH (n=150)
Age at admission to CCU, y ± SD	50.55 ± 1.42	50.21 ± 0.58
LDL cholesterol at admission, mmol/L ± SD	3.82 ± 0.24	3.30 ± 0.09
Untreated LDL cholesterol, mmol/L ± SD	6.49 ± 0.26	3.73 ± 0.08
Male, % (95% CI)	72.0 (53.1-90.9)	82.0 (75.8-88.2)
Diabetes, % (95% CI)	32.0 (12.3-51.7)	18.7 (12.4-25.0)
Hypertension, % (95% CI)	48.0 (27.0-69.0)	46.0 (37.9-54.1)
Obesity, % (95% CI)	16.0 (5.6-31.4)	11.3 (6.2-16.5)
Current or ex-smoking, % (95% CI)	40.0 (19.4-60.6)	54.7 (46.6-62.7)

Bibliographic reference	Pang 2015
	Use of statins, % (95% CI) | 68.0 (48.3-87.7) | 21.3 (14.7-28.0)
Source of funding	The Australian Better Health Initiative and the Department of Health
Comments	Individuals on statins had their plasma LDL cholesterol conservatively adjusted by a correction factor that depends on the dose and potency of specific statins to estimate the pre-treatment levels. Good paper. Sample may have been biased as all patients recruited from an inpatient CCU.

Taylor 2010

Bibliographic reference	Taylor 2010
Study type	Prospective/ reported in Letter
Aim	To describe a rapid, stepwise screening strategy to screen for mutations in patients with FH in the UK.
Patient characteristics	Adult and paediatric patients; 19 definite FH, 91 possible FH
Number of patients	110 people from lipid clinics
Index test	Simon Broome criteria
Reference standard (or Gold standard)	Genetic test
Time between testing & treatment	n/a
Length of follow-up	n/a
Location	UK
Results	Mutation detected in 43/110, 63.2% in definite FH, 34% in possible FH % reported in paper, n calculated by analyst

Mutation	Possible FH n=91	Definite FH, n=19
ARMS	20%, n=18	32%, n=6
LDLR	12%, n=11	21%, n=4
LDLR MLPA rearrangement	2%, n=2	10%, n=2
No mutation	66%, n=60	37%, n=7

Source of funding	DoH, department of trade and industry, London IDEAS genetic knowledge park.
Comments	CASP:

Bibliographic reference	Taylor 2010
	Results valid, lack of detail on study population; unclear how many adults and children.

Wald 2015

Bibliographic reference	Wald 2015
Study type	Cohort
Aim	To report prevalence of DNA confirmed FH in young patients with acute MI, relative contribution of smoking and diabetes and to compare those rates with those
Patient characteristics	Patients with MI, admitted to hospital
Number of patients	3076 people with acute MI admitted to hospital; 240 underwent DNA analysis
Index test	FH48 panel, bidirectional sanger sequencing, entire LDLR gene coding region
Reference standard (or Gold standard)	n/a
Time between testing & treatment	n/a
Length of follow-up	n/a
Location	UK
Results	3/231 FH cases diagnosed Between June 2011 and April 2013; 3076 patients with acute MI admitted to hospital and 474 were aged 50 or less. 240 underwent DNA analysis; 66 declined testing 43 did not speak English 35 were too unwell 90 were not offered testing because they were weekend admissions. DNA analysis failed in 9 patients
Source of funding	Barts and the London Charity service enhancement grant
Comments	Appropriate DNA sequencing

Widhalm 2007

Bibliographic reference	Widhalm 2007
Study type	Prospective cohort

<table>
<tr><th>Bibliographic reference</th><th>Widhalm 2007</th></tr>
<tr><td>Aim</td><td>To compare conventional MED-PED criteria with DNA analysis for diagnosis of familial hypocholesteraemia in children, adolescents and their relatives.</td></tr>
<tr><td>Patient characteristics</td><td>

Patients with premature atherosclerosis and/or hypercholesterolemia – children and adolescents less than 18 years and their families were referred to the lipid clinic by either general practitioners or hospital specialists because a member of the family was suffering from early CVD (<50 years) or had died due to MCI or stroke at an early age (<50 years). Others were noticed incidentally as presenting elevated serum lipid levels during checking of routine blood parameters. Some families came on their own initiative asking for further information on FH.
116 children – 57 girls; 59 boys; mean age: 11.6 (4.1); mean LDL-C in mg/dl: 198 (67)
147 adults – 4 women; 83 men;
Mean age for women 41.5 (13.7); mean LDL-C in mg/dl: 210 (67)
Mean age for men 42.8 (10.8); mean LDL-C in mg/dl: 233 (83)
Definite (where the family had a t least one member with confirmed FH) and possible FH (whose family had no member with proven FH) included

</td></tr>
<tr><td>Number of patients</td><td>N=263 from 148 families</td></tr>
<tr><td>Index test</td><td>MED-PED criteria (make early diagnosis; prevent early death): the criteria are recommended for patients to confirm diagnosis in so-called index patients (IPs) and for relatives of index patients (rIPs).</td></tr>
<tr><td>Reference standard (or Gold standard)</td><td>DNA analysis: whole blood taken for LDLR gene analysis by DNA isolation, PCR and denaturing gradient gel electrophoresis</td></tr>
<tr><td>Time between testing & treatment</td><td>Not reported</td></tr>
<tr><td>Length of follow-up</td><td>Not reported</td></tr>
<tr><td>Location</td><td>Austria</td></tr>
<tr><td>Results</td><td>Genetic diagnosis:
N=116
N=57 children
N= 62 adults

Diagnosis according to MED-PED (% of genetic diagnosis presented only, n calculated by analyst):
<table>
<tr><td></td><td>Adults (n=147)</td><td>Children (n=116)</td></tr>
<tr><td>Criteria for index case</td><td>16</td><td>19</td></tr>
<tr><td>Criteria for relative of index case</td><td>20</td><td>33</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Widhalm 2007		
	Do not meet criteria	22	11
Source of funding	Not reported		
Comments	• Unclear numbers presented for MEDPED diagnosis – only % presented. • All patients with confirmed FH received a special diet low in saturated fats and rich in monounsaturated fats using rapeseed oil.		

Wald 2016

Bibliographic reference	Wald 2016
Study type	Prospective cohort
Aim	To assess the efficacy and feasibility of child parent screening for FH in primary care practice.
Patient characteristics	Male,n (%) 5213 (52%); median age (IQR) 12.7 months (12.4, 13.3); family history of premature MI, n (%) 1094 (11%)
Number of patients	10,095 children aged 1-2 years.
Index test	Genetic testing for LDLR, APOB, PCSK9
Reference standard (or Gold standard)	N/A
Time between testing & treatment	N/A
Length of follow-up	N/A
Location	92 GP practices, UK
Results	Blood sample taken from heel stick sample of capillary blood. Total cholesterol, HDL and triglyceride levels were measured, LDL initially calculated by the Friedwald equation, and later independently calculated at the study centre. LDL converted to multiples of the median (MoM) for all children screened. Median value from a pilot study used initially and was updated after every 2000 measurements. Children who had a cholesterol level at least 1.53 MoM and also had a FH mutation or cholesterol level of at least 1.53MoM on the repeat test were considered to have positive screening results for FH. The parent was classified as having FH if they had the same mutation as the child, or if they had a high cholesterol level. Cholesterol level was at least 1.53MoM in 92 children; 20 people had an FH mutation. Cholesterol level was less than 1.53MoM. 17 had an FH mutation. (37 mutations in 10095 children)

Bibliographic reference	Wald 2016
	Parents of 32 children tested for FH (5 unavailable or did not consent) 28 parents identified when using cut-off of 1.53 MoM used 40 parents identified when cut-off of 1.35 MoM used.
Source of funding	Supported by the medical research council
Comments	23 incorrect results (<0.3%) found to be a result of transcription errors, were identified and excluded from the analyses. (original sample size 10,118). The use of MoM helps to overcome analytic differences among instruments and avoids imprecision in the estimation of extreme percentile cut-offs in new populations. Study used different cut-offs for MoM measurements to assess how many detected. Also used 1.35MoM (95th %) + mutation or two cholesterol values of at least 1.50MoM (99th %) which identified 40 children who had positive screening results for FH (32 with mutation and 8 without mutation) and 40 parents with positive screening results for FH. Unclear whether parents had genetic testing – no results available in paper. Did not use recognised scoring criteria (e.g. SB or DLCN)

G.2 Diagnosis

Please see appendix G1 for evidence tables for Bell (2014), Bell (2014a), Clarke (2013), Futema (2013), Hralambos (2015), Jannes (2015) and Kirke (2015).

Hooper 2012

Bibliographic reference	Hooper A J, Nguyen L T, Burnett J R, Bates T R, Bell D A, Redgrave T G, Watts G F, van Bockxmeer , and F M. (2012). Genetic analysis of familial hypercholesterolaemia in Western Australia. Atherosclerosis, 224(2), pp.430-4
Study type	Prospective cohort
Aim	To determine the spectrum of mutations associated with FH and their detection rate in the FH western Australia program
Patient characteristics	Consecutive patients considered to have phenotypic FH referred for DNA testing at Lipid Disorders Clinic at Royal Perth Hospital.
Number of patients	N=343 (337 had DLCN score available)
Index test	DLCN score (phenotypic details only) >8: definite

Bibliographic reference	**Hooper A J, Nguyen L T, Burnett J R, Bates T R, Bell D A, Redgrave T G, Watts G F, van Bockxmeer , and F M. (2012). Genetic analysis of familial hypercholesterolaemia in Western Australia. Atherosclerosis, 224(2), pp.430-4**
	6-8: probable 3-5:possible >3: unlikely
Reference standard (or Gold standard)	Genetic testing for mutations in LDLR, APOB and PCSK9.
Time between testing & treatment	N/A
Length of follow-up	N/A
Location	Western Australia
Diagnostic accuracy measures (2 x 2 table)	129 people had mutations identified in 343 people referred for genetic testing Distribution of DLCN scores

DLCN score	N (337) (n calculated by analyst)	N with mutation (n calculated by analyst)
>8: definite	128 (38%)	90 (70%)
6-8: probable	88 (26%)	26 (29%)
3-5:possible	111 (33%)	12 (11%)
>3: unlikely	10 (3%)	

Source of funding	Grants from the Health Department of Western Australia and University of Western Australia
Comments	None

Maglio 2014

Bibliographic reference	**Maglio C, Mancina R M, Motta B M, Stef M, Pirazzi C, Palacios L, Askaryar N, Boren J, Wiklund O, and Romeo S. (2014). Genetic diagnosis of familial hypercholesterolaemia by targeted next-generation sequencing. Journal of Internal Medicine, 276(4), pp.396-403.**
Study type	Prospective cohort
Aim	To combine clinical criteria and NGS to establish a diagnosis of FH
Patient characteristics	Adults with DLCN score ≥3 (possible, probable or definite FH). Male 38 (49%); mean age 51 (14) years; mean pre-treatment LDL-C 6.9 (1.7) mmol/L; Dutch score ≥6 (definite or probable FH 57 (74%)

Bibliographic reference	**Maglio C, Mancina R M, Motta B M, Stef M, Pirazzi C, Palacios L, Askaryar N, Boren J, Wiklund O, and Romeo S. (2014). Genetic diagnosis of familial hypercholesterolaemia by targeted next-generation sequencing. Journal of Internal Medicine, 276(4), pp.396-403.**
Number of patients	77
Index test	DLCN score ≥3
Reference standard (or Gold standard)	NGS for LDLR, APOB and PCSK9.
Time between testing & treatment	N/A
Length of follow-up	N/A
Location	Sweden
Diagnostic accuracy measures (2 x 2 table)	50/77 people had mutation detected.
Source of funding	Swedish Research Council, Swedish Diabetes foundation, Swedish heart-lung foundation, regional agreement on medical training and clinical research, Wilhelm and Martina Lundgren Science fund and Nilsson-Ehle funds.
Comments	No detail on number of mutations found in DLCN subgroups e.g. possible, probable or definite separately. Cannot calculate sensitivity and specificity as all participants had DLCN and no distinction as to definite, probable or possible.

G.3 Management (statin monotherapy)

McCrindle 2002

Bibliographic reference	McCrindle BW1, Helden E, Cullen-Dean G, et al. (2002) A randomized crossover trial of combination pharmacologic therapy in children with familial hyperlipidemia. Pediatr Res.. 51(6):715-21.
Study type	Randomised, open label, crossover
Aim	To determine whether a low-dose combination of a bile-acid – binding resin (coletipol) with pravastatin would result in improved acceptability, compliance and effectiveness in lipid-lowering compared with conventional therapy of colestipol only at a higher dose.
Patient characteristics	Aged 8 -18 yrs, positive family history of hypercholesterolaemia or premature artherosclerotic cardiovascular disease in first-degree relatives. No significant differences between groups. All patients instructed to stop takeing any lipid lowering medications at least 8 weeks before start of study.

	Colestipol only (n=16)	Colestipol + pravastatin (n=20)

Bibliographic reference	McCrindle BW1, Helden E, Cullen-Dean G, et al. (2002) A randomized crossover trial of combination pharmacologic therapy in children with familial hyperlipidemia. Pediatr Res.. 51(6):715-21.

Male: female	11:5	14:6
Age, Median (range)	14 (10,18)	14 (9,18)
Family history of father with hyperlipidaemia	12/15 (80%)	12/18 (67%)
Family history of father with CV event	6/15 (40%)	6/18 (33%)
Family history of mother with hyperlipidaemia	7/15 (47%)	7/18(39%)
Mean fasting LDL-C (mM/L)	5.91 (1.20)	6.37 (1.50)
Mean TC (mM/L)	7.61 (1.26)	8.32 (1.52)

Number of Patients	N=36
Intervention	Colestipol (5g) + pravastatin (10mg) All patients adhered to American Heart Association type 2 diet throughout the study.
Comparison	Colestipol (10g per day) All patients adhered to American Heart Association type 2 diet throughout the study.
Length of follow up	2 x 18 week medication periods with an intervening 8 week washout period.
Location	Canada
Outcomes measures and effect size	

LDL-C (mM/L), mean (SD)	Colestipol only	Colestipol + pravastatin
Absolute change	-0.65 (0.80)	-1.07 (1.06)
Relative change (%)	-9.9 (13.4%)	-16.8 (15.8)*

*p<0.05

Adverse events: reported as % of people causing constipation/ bloating or gas/ stomach ache/ headache/ muscle ache. Higher % in colestipol only group for all AEs. NR whether significant.

Compliance from counts of returned unused medication (mean, SD) [expressed as % of medication presumed taken vs dose prescribed]

	Colestipol only (10g/d)	Colestipol (5g/d)	Pravastatin (10mg/d)
First 8 week	63 (29)	66 (27)	65 (26)

Bibliographic reference	McCrindle BW1, Helden E, Cullen-Dean G, et al. (2002) A randomized crossover trial of combination pharmacologic therapy in children with familial hyperlipidemia. Pediatr Res.. 51(6):715-21.
	Second 10 week: 57 (44); 58 (33); 60 (39) total: 60 (31); 62 (27); 62 (28)
Source of funding	NR
Comments	Randomisation stratified by 2 centres, random blocks of 4, 6 and 8 using a random number generator. Sample size required calculated as 40.

Vuorio 2014

Bibliographic reference	Vuorio A, Kuoppala J, Kovanen PT et al. (2014) Statins for children with familial hypercholesterolemia. Cochrane Database of Systematic Reviews CD006401.
Study type	Cochrane systematic review: 4 of 8 studies included in analysis. Randomised and non-randomised but controlled inical studies with systematic allocation.
Aim	To assess the effectiveness and safety associated with the use of statins in children heterozygous for FH.
Patient characteristics	Children and adolescents up to 18 yrs at start of study,
Number of Patients	4 studies (Knipscheer 1996; Wiegman 2004; McCrindle 2003; Avis 2010)
Intervention	Active treatment with a statin (lovastatin, simvastatin, pravastatin, fluvastatin, rosuvastatin, atorvastatin) The Cochrane review included all statin types, this review specified only fluvastatin, rosuvastatin, atorvastatin, therefore 4 studies reporting on other statins not included, listed in comments below.
Comparison	Control treatment with another statin, or with placebo or with other lipid-lowering agents, or with diet alone or with no treatment.
Length of follow up	Median 24 weeks (range 6 weeks – two years)
Location	Various
Outcomes measures and effect size	Change in serum LDL-Cholesterol level (%)

Study	Statins, mean change (SD)	Placebo, mean change (SD)
Knipscheer (1996)	-22 (10)	-3 (13)
Wiegman (2004)	-23.8 (16.7)	0 (15.2)

Liver dysfunction

a. Change in aspartate aminotransferase levels, 3 x ULN (n)

	Statins	Placebo

Bibliographic reference	Vuorio A, Kuoppala J, Kovanen PT et al. (2014) Statins for children with familial hypercholesterolemia. Cochrane Database of Systematic Reviews CD006401.

Knipscheer (1996)	0/54	0/18
Wiegman (2004)	0/104	2/107

b. Change in alanine aminotransferase levels, 3 x ULN (n)

	Statins	Placebo
Wiegman (2004)	0/104	0/107

Change in serum creatine kinase levels (myopathy), 10 x ULN (n)

	Statins	Placebo	RR (95%CI)
Avis (2010); Knipscheer (1996)	4/167	0/60	3.23 (0.18, 38.84

Rhabdomyolysis-NR

Myocardial infarction-not reported in any study.

Compliance: Wiegman (2004) reported that children adhered to the protocol (84% of tablets among children studied were taken for full 2 years of study)

Adverse events.

	Statins	Placebo	RR (95%CI)
At 1 month	83/184	34/64	0.86 (0.65, 1.13)

Source of funding	Not reported
Comments	Stein 1999; Clauss 2005; Couture 1988; de Jongh 2002a excluded as simvastatin and lovastatin were interventions. Only data from included studies reported here. Other primary outcomes in Cochrane were change in thickness of carotid intima, change in measures of growth and maturation. Other secondary outcomes were change in endothelial function, change in serum total, HDL and triglyceride levels, quality of life

Appendix H: Forest plots

H.1 Case finding

No forest plots

H.2 Diagnosis

Figure 1: Sensitivity and specificity of possible and definite Simon Broome criteria to detect genetic FH

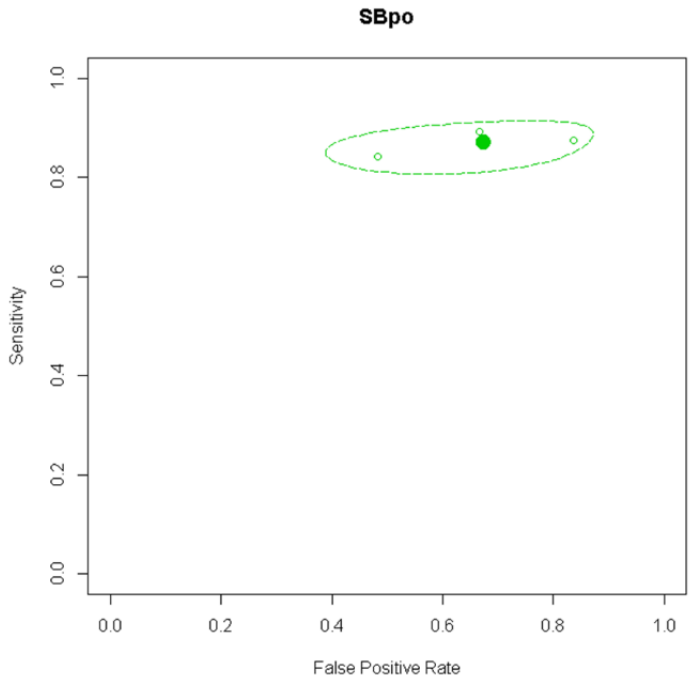


Figure 2: Sensitivity and specificity of definite Simon Broome criteria to detect genetic FH

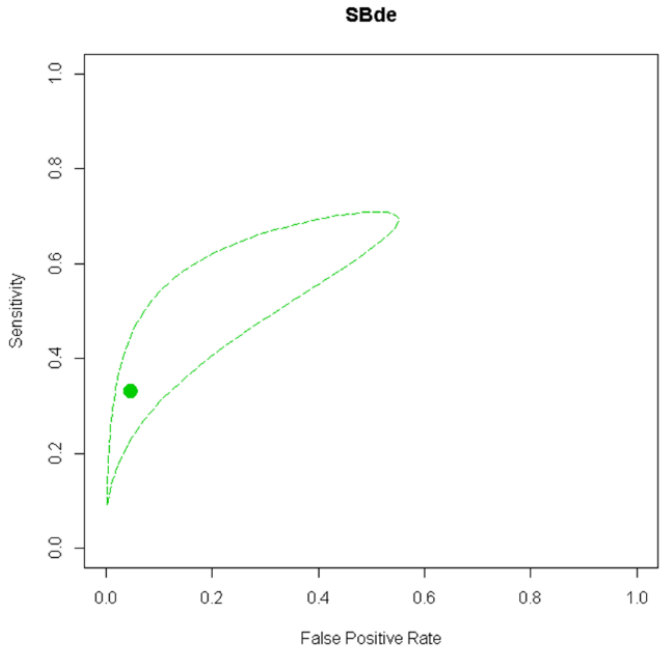


Figure 3: Sensitivity and specificity of possible, probable and definite DLCN criteria (score >2) to detect genetic FH

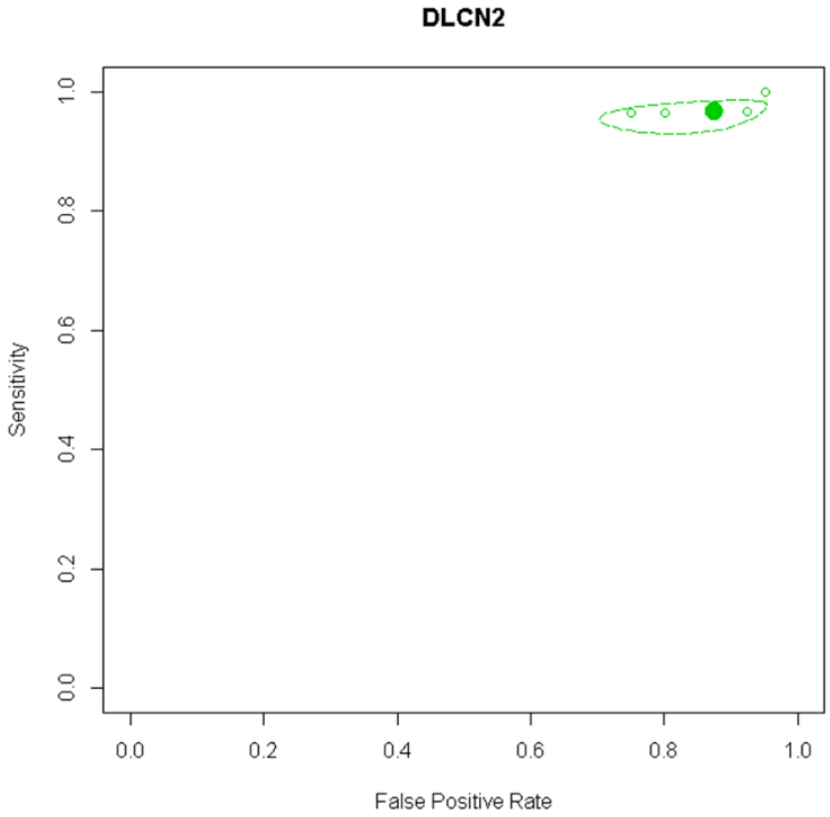


Figure 4: Sensitivity and specificity of probable and definite DLCN criteria (score >5) to detect genetic FH

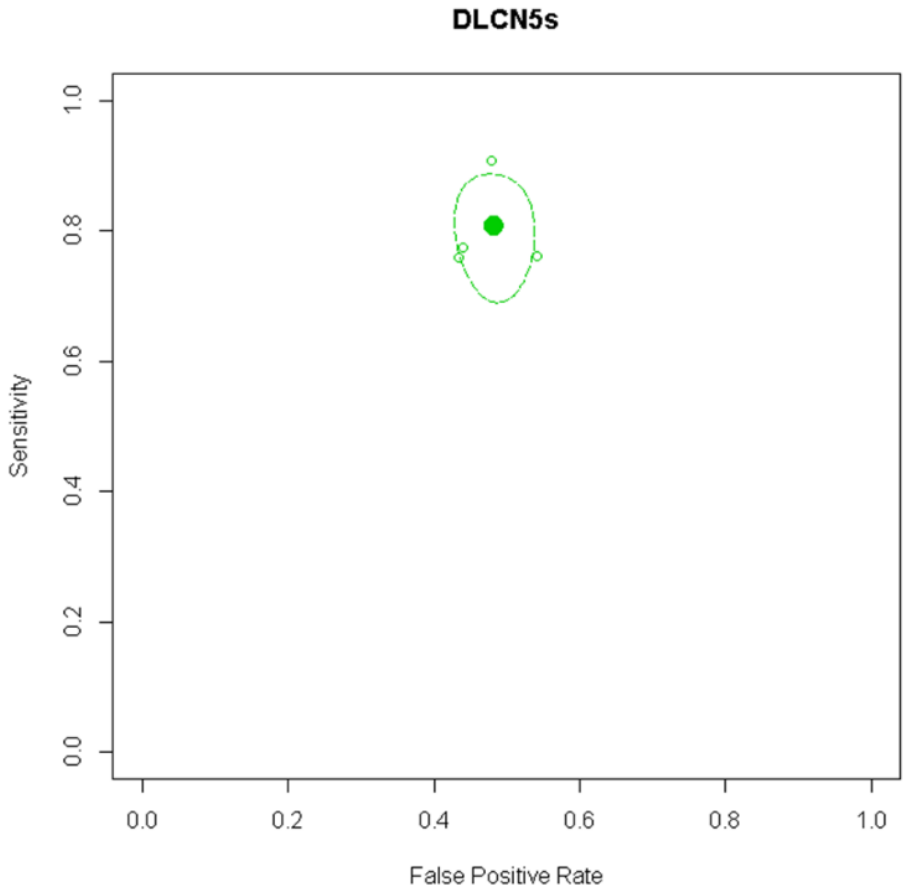
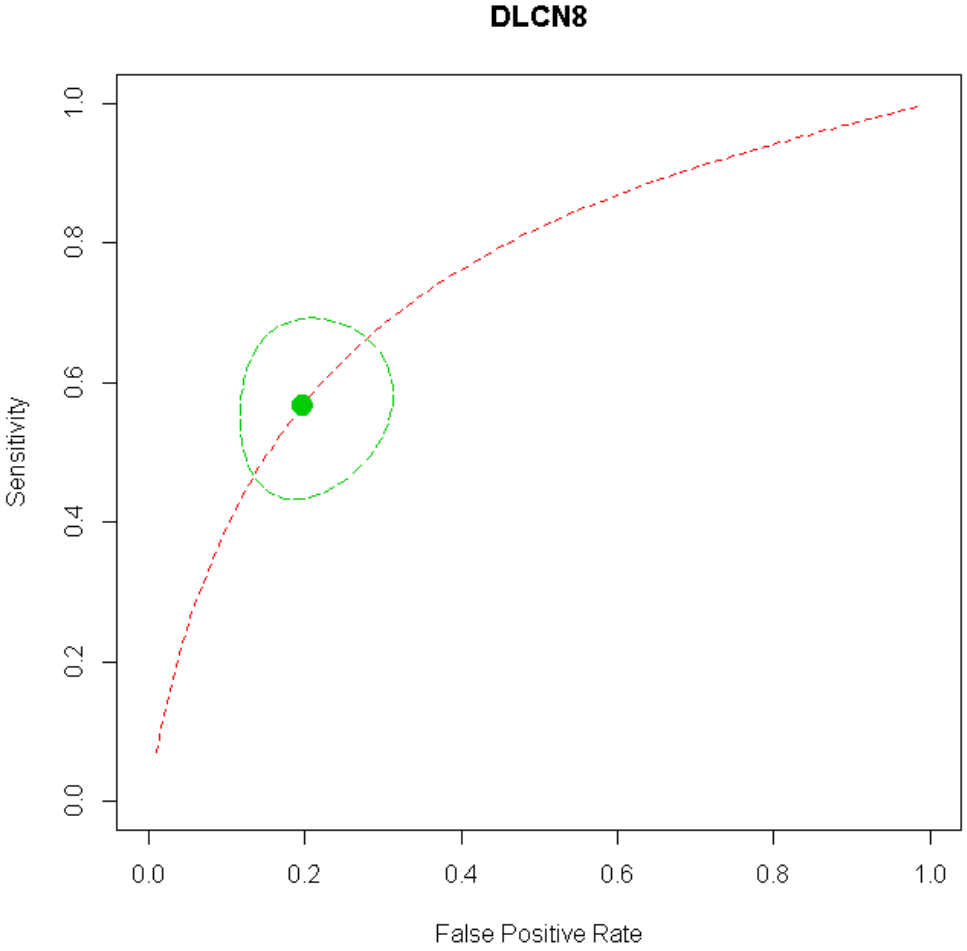


Figure 5: Sensitivity and specificity of definite DLCN criteria (score >8) to detect genetic FH



H.3 Management (statin monotherapy)

Figure 6: Change in LDL-C concentration (%)

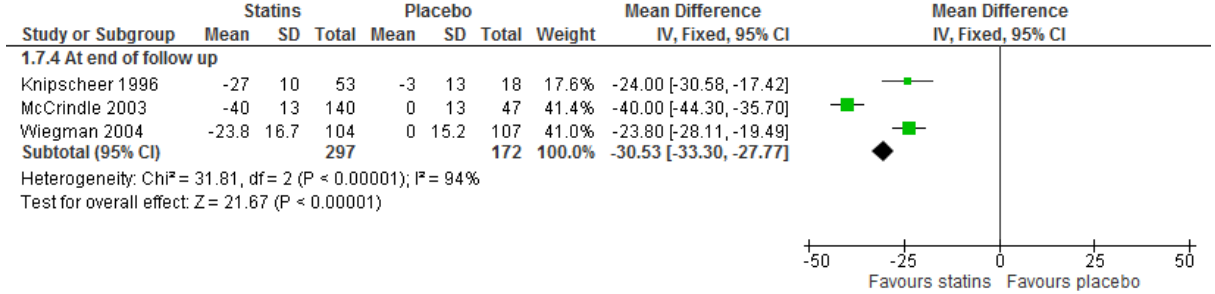


Figure 7: Adverse events

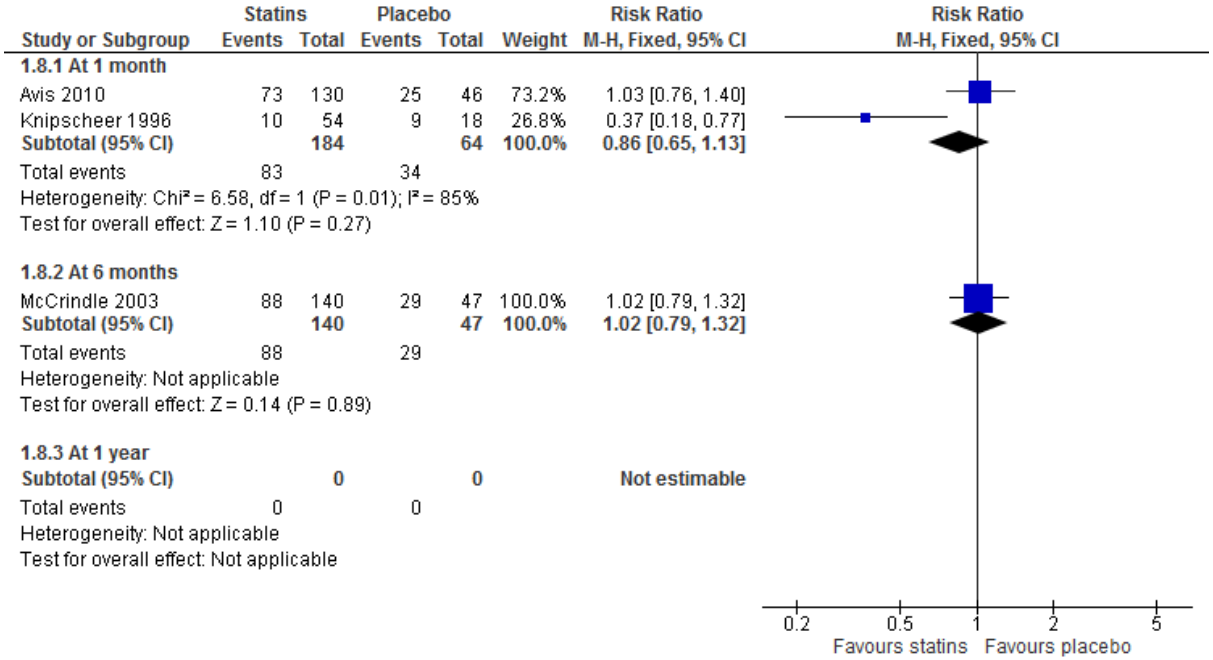


Figure 8: Change in aspartate aminotransferase (x3 ULN)

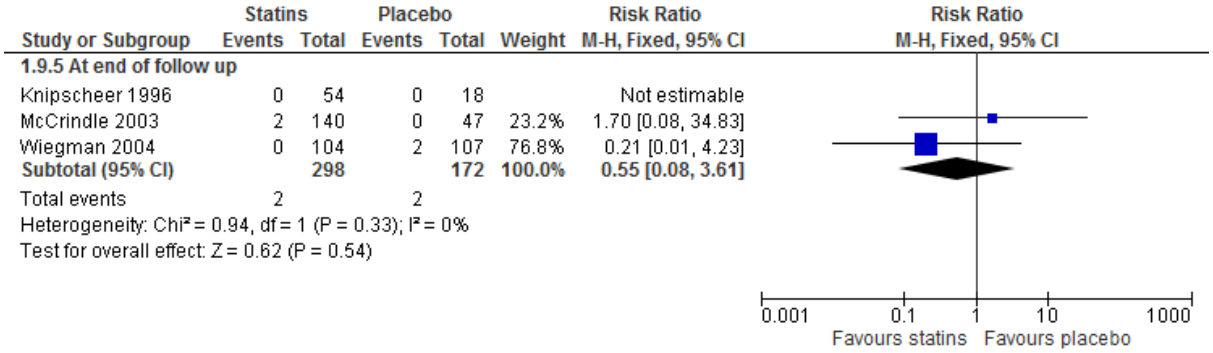


Figure 9: Change in alanine aminotransferase (x3 ULN)

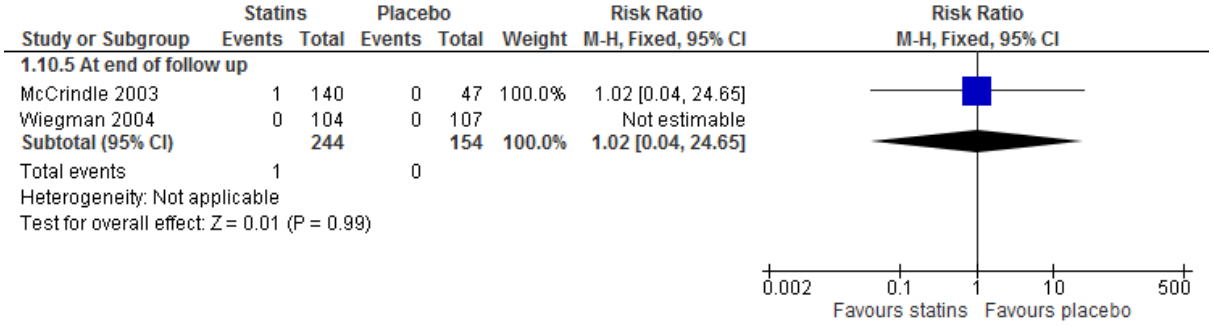


Figure 10:Myopathy: change in CK (x10 ULN)

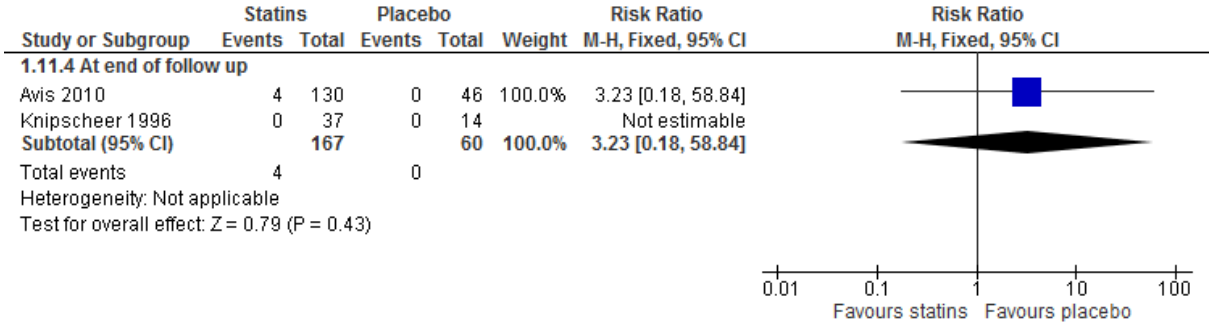
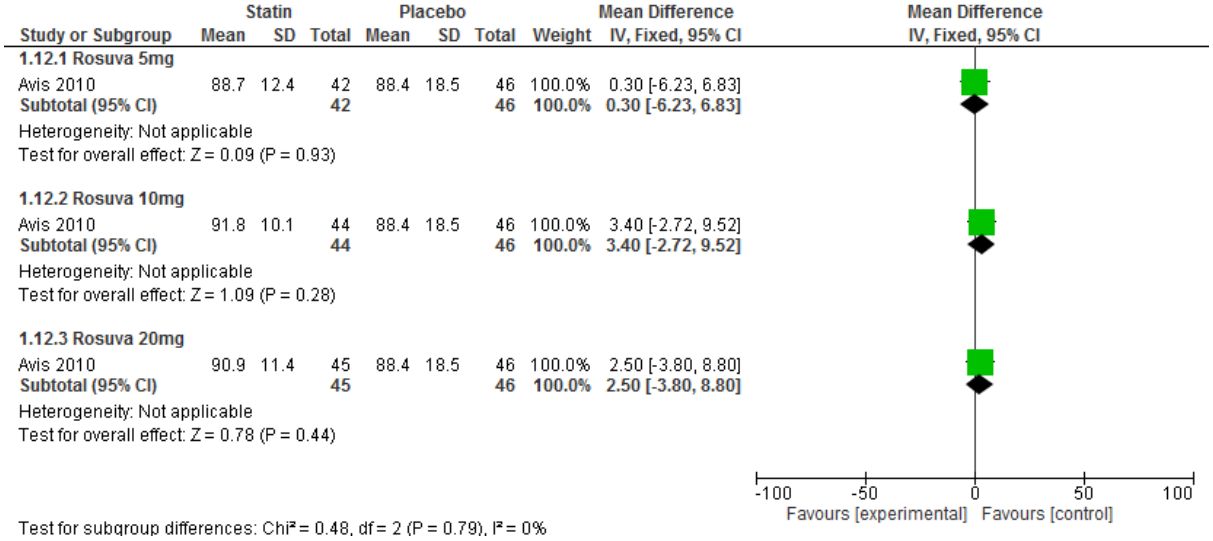


Figure 11:Compliance (%)



Appendix I: GRADE profiles

I.1 Case-finding

I.1.1 Cascade testing

Table 26: Cascade testing: Diagnostic yield for genetic and clinical diagnoses and uptake rate.

Quality assessment							No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	N with FH	N tested	Median (range)	
Outcome: Diagnostic yield from clinical diagnosis of FH in direct cascade testing: Adults (SB, DLCN criteria)										
2	1 case series, 1 prospective cohort	Very serious[6]	No serious	Not applicable[4]	Cannot be assessed[5]	none	133	405	6.0 – 59.0%*	Very low
Outcome: Diagnostic yield from clinical diagnosis of FH in indirect cascade testing: Adults (medped, other clinical diagnostic criteria)										
2	Case series	Very serious[1]	No serious	Not applicable[4]	Cannot be assessed[5]	none	289	776	30.5 -37.9%*	Very low
Outcome: Diagnostic yield from clinical diagnosis of FH in indirect and direct cascade testing: Adults (SB criteria)										
2	Prospctive cohort	Serious[3]	No serious	Not applicable[4]	Cannot be assessed[5]	none	440	1,879	14.7 -57.5%*	Low
Outcome: Diagnostic yield from genetic cascade testing (direct)										
5	4 case series, 1 prospective cohort	Very serious[8]	Serious[2]	Not applicable[4]	Cannot be assessed[5]	none	2,636	7,144	37.5% (11.4 -51.4%)	Very low

Quality assessment							No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	N with FH	N tested	Median (range)	
Outcome: Diagnostic yield from genetic cascade testing (indirect)										
1	Case series	Very serious[1]	No serious	Not applicable[4]	Cannot be assessed[5]	none	808	1,805	44.8%	Very low
Outcome: Diagnostic yield from genetic cascade testing (direct and indirect)										
1	Prospective cohort	No serious	No serious	Not applicable[4]	Cannot be assessed[5]	none	359	642	55.9%	Moderate
Outcome: Diagnostic yield from genetic cascade testing (unknown methods)										
2	1 case series, 1 prospective cohort	Very serious[7]	Very serious[7]	Not applicable[4]	Cannot be assessed[5]	none	958	2,910	32.8 -33.9%*	Very low
Outcome: Uptake rate of testing-direct cascade testing: index individuals										
3	1 case series, 2 prospective cohort sl	Very serious[2]	No serious	Not applicable[4]	Cannot be assessed[5]	none	1,208	1,557	84.1% (69.1 -98.9%)	Very low
Outcome: Uptake rate of testing--direct cascade testing: relatives of index individuals										
2	1 case series, 1 prospective cohort	Very serious[6]	No serious	Not applicable[4]	Cannot be assessed[5]	none	563	582	84.1 -98.9%*	Very low
Outcome: Uptake rate of testing-indirect cascade testing: relatives of index individuals										

Quality assessment							No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	N with FH	N tested	Median (range)	
1	Case series	Very serious[1]	No serious	Not applicable[4]	Cannot be assessed[5]	none	1,805	2,474	73.0%	Very low
Outcome: Uptake rate of testing-both indirect and direct cascade testing: relatives of index individuals										
1	Prospe ctive cohortl	Serious[3]	No serious	Not applicable[4]	Cannot be assessed[5]	none	1,494	2,292	65.2%	Low

**where only 2 studies report an outcome only the range is reported, as median cannot be calculated from two studies or less.*

1. *Leren (2008) assumes that all those with low serum cholesterol did not have clinical FH, did not take account of those on lipid lowering therapy at time of testing. Judged that concerns did not affect results as study results not at extremes of range. PCSK9 mutation not tested for. Leren (2008) and Marks (2006) both case series studies and therefore quality starts at low.*
2. *Thorsson (2003) indirect population; study undertaken in Iceland using family tracing methods that would not be applicable to UK population. Bhatnager (2000) was a case series study and therefore low quality.*
3. *Hadfield (2009) no data on first degree relatives FDRs known to have FH not included.*
4. *Data from the studies was not pooled, therefore judged as no serious inconsistency, not downgraded.*
5. *Imprecision could not be formally assessed because median and range were reported. Downgraded 1 level due to the resulting uncertainty around the precision of the estimate.*
6. *Taylor (1993) included a population of children only; does not use standardised diagnostic criteria (e.g. DLNC), relies on clinical criteria only. Taylor (1993), unable to tell whether authors identified all confounding factors; unclear whether follow up complete. Bhatnager (2000) is a case series study and therefore starts at low quality.*
7. *Vergoline (2001) undertaken in South African population, looking for Afrikaner foundation mutations, unclear whether applicable to UK population. Lee (1998) did not undertake full genetic testing, only LDLR gene mutations. Vergoline (2001) was a case series study, therefore low quality.*
8. *Four studies contributing to the outcome were case series and one was a prospective cohort, therefore low quality.*

I.1.2 Primary care

No GRADE profiles were produced for this question, as a narrative quality assessment is reported in the evidence review (section 2.3.2).

I.1.3 Secondary care

Table 27: Secondary care: Diagnostic yield and uptake rate:

Quality assessment							No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	N with FH	N tested for FH	Median (range)	
Outcome: Diagnostic yield – clinical diagnosis FH: pathology databases (Bell 2012, Bell 2014 and Kirke 2015)										
3	1 case series, 2 prospective cohorts	Very serious[1, 11]	No serious	Not applicable[9]	Cannot be assessed [10]	none	1045	85,616	8.5% (1.2-9.2%)	Very low
Outcome: Diagnostic yield – clinical diagnosis FH: lipid clinics or registries (Chung 1999, Haralambos 2015, Widhalm 2007 and Hu 2013)										
4	2 case series, 2 prospective cohorts	Very serious[2]	No serious	Not applicable[9]	Cannot be assessed [10]	none	892	1343	51.0% (33.5 – 87.8%)	Very low
Outcome: Diagnostic yield – clinical diagnosis FH: coronary care units/ MINAP (Bates 2008, De Backer 2015, Nanchen 2015, Pang 2015)										
4	Prospective cohort	No serious[3]	No serious	Not applicable[9]	Cannot be assessed [10]	none	694	12,331	5.9% (1.2 – 14.3%)	Moderate
Outcome: Diagnostic yield – clinical diagnosis FH: screening (Beeso 1999, Wald 2016)										
2	Prospective cohort	Very serious[4]	Serious[4]	Not applicable[9]	Cannot be assessed [10]	none	22	19,768	0.001-0.145%*	Very low
Outcome: Diagnostic yield – genetic diagnosis FH: pathology databases (Kirke 2015, Muir 2010, Bell 2014)										

Quality assessment							No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	N with FH	N tested for FH	Median (range)	
3	2 case series, 1 prospective cohort	Serious[1, 5, 11]	No serious	Not applicable[9]	Cannot be assessed [10]	none	91	641	26.7% (12.9 -30.4%)	Very low
Outcome: Diagnostic yield – genetic diagnosis FH: lipid clinics or registries (Futema 2013, Heath 2001, Medeiros 2010, Taylor 2010, Widhalm 2007)										
6	3 case series, 2 prospective cohorts	Very serious[6]	No serious	Not applicable[9]	Cannot be assessed [10]	none	700	1,955	33.3% (10.9 -51.0%)	Very low
Outcome: Diagnostic yield – genetic diagnosis FH: coronary care units/ MINAP (Wald, 2015)										
1	Prospective cohort	Serious[7]	Serious	Not applicable[9]	Cannot be assessed [10]	none	3	231	1.2%	Low
Outcome: Diagnostic yield – genetic diagnosis FH: screening (Laurie 2004, Klancar 2015; Wald 2016)										
3	2 case series, 1 prospective cohort	Very serious[8]	Serious[8]	Not applicable[9]	Cannot be assessed [10]	none	203	10,432	17.0% (0.4, 57.0%)	Very low
Outcome: Uptake rate of FH testing: pathology databases (Bell 2014, Kirke 2015)										
Increased CV risk attending clinical	1 case series, 1 prospe	Very serious[1, 11]	No serious	Not applicable[9]	Cannot be assessed [10]	none	Increased CV risk attending clinical assessme	Increased CV risk attending clinical	Increased CV risk attending clinical assessment for FH: 13.2%	Very low

Quality assessment							No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	N with FH	N tested for FH	Median (range)	
assessment for FH: 1 Attending specialist review: 2	ctive cohort						nt for FH: 597 Attending specialist review: 53	assessment for FH: 4517 Attending specialist review: 86	Attending specialist review: 61.6%	
Outcome: Uptake rate of FH testing: coronary care units/ MINAP (Wald 2015)										
1	Prospective cohort	No serious	Serious[7]	Not applicable[9]	Cannot be assessed [10]	none	240	474	50.1%	Low
Outcome: Uptake rate of FH testing: screening (Beeso 1999)										
1	Prospective cohort	Serious[4]	Serious[4]	Not applicable[9]	Cannot be assessed [10]	none	82	189	43.4%	Very low

**where only 2 studies report an outcome only the range is reported, median cannot be calculated for 2 or fewer studies*

1. *Bell (2012) used Medped, Simon Broome, DLNC and >6.5 mmol/L as criteria to diagnose FH, mean value used for quality assessment; Simon Broome criteria significantly higher diagnostic rate (3.68%) compared to other 3 methods (mean 0.306%). Bell (2014)was a case control study where efficacy of telephone call by chemical pathologist in diagnosing FH*
2. *Chung (1999) is small study (n=11) with an indirect ethnic population (Chinese), case series; Hu (2013) is also in an indirect ethnic population and a case series design; Widhalm (2007) had population with early CVD, or family history of early CVD or high serum cholesterol; study does not report how many index patients or relatives diagnosed, different medped criteria used for these groups, molecular method of diagnosis unclear.*
3. *Bates (2008) does not use molecular methods to confirm diagnosis, but quality not down-graded as relatively small study contributing to overall effect.*
4. *Beeso (1999) population of neonates only; used apolipoprotein A1: B ratio to assess presence of FH.*
5. *Muir (2010) identified people on basis of raised TC (>8mmol/L) not raised LDL-C, case series design.*
6. *Widhalm (2007) had population with early CVD, or family history of early CVD or high serum cholesterol; study does not report how many index patients or relatives diagnosed, different medped criteria used for these groups, molecular method of diagnosis unclear. Taylor (2010) had population already diagnosed with definite FH according to Simon Broome criteria. Futema (2013) had population diagnosed with FH according to Simon Broome criteria, case series design. Medeiros (2010) reporting of numbers included and diagnosed unclear. Heath (2001) population was people with FH using SB criteria, did not report n of children included; Heath (2001) using old, insensitive method therefore not reliable outcome, case series design. Haralambos (2015) used adapted Dutch Lipid criteria (welsh criteria) to assess FH.*
7. *Wald (2015) is a relatively small study.*

8. *Laurie (2004) had population with TC >8 mmol/L, lack of detail about study. Laurie (2004) and Klancar (2015) small studies with identification methods not applicable to UK, both case series design.*
9. *Data from the studies was not pooled, therefore judged as no serious inconsistency, not downgraded.*
10. *Imprecision could not be formally assessed because median and range were reported. Downgraded 1 level due to the resulting uncertainty around the precision of the estimate.*
11. *Kirke (2015) identified patients from a pathology laboratory – very low uptake rate for further testing amongst people at high risk of FH.*

I.2 Diagnosis

Table 28: Diagnostic accuracy of Simon Broome and DLCN criteria to identify genetic FH

Number of studies	Number of participants	Risk of bias	Indirectness	Inconsistency	Imprecision	TP	FP	FN	TN	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	GRADE quality
Index test 1: Simon Broome possible + definite												
4	1,872	VS[2]	S	VS[4]	NS	494	817	61	290	0.890 (0.845, 0.924)	0.287 (0.160, 0.459)	Very low
Index test 2: Simon Broome possible + definite – sensitivity analysis (without Haralambos 2015 data)												
3	656	NS	NS	VS[4]	VS[1]	384	102	36	134	0.870 (0.825, 0.905)	0.325 (0.173, 0.526)	Very low
Index test 3: Simon Broome definite												
4	1,872	VS[2]	S	VS[4]	VS[3]	252	132	363	1125	0.360 (0.186, 0.581)	0.86 (0.158, 0.995)	Very low
Index test 4: Simon Broome definite – sensitivity analysis (without Haralambos 2015 data)												
3	666	NS	NS	VS[4]	VS[3]	107	36	173	350	0.335 (0.156, 0.578)	0.804 (0.073, 0.995)	Very low
Index test 5: DLCN possible, probable and definite (score>2)												
4	936	NS	NS	VS[4]	NS	403	462	10	61	0.967 (0.939, 0.983)	0.125 (0.057, 0.253)	Low
Index test 6: DLCN probable and definite (score>5)												

Number of studies	Number of participants	Risk of bias	Indirectness	Inconsistency	Imprecision	TP	FP	FN	TN	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	GRADE quality
4	1,531	NS	NS	VS[4]	NS	501	592	82	356	0.868 (0.711, 0.946)	0.457 (0.320, 0.601)	Low
Index test 7: DLCN probable and definite (score>5) -sensitivity analysis (without Haralambos data)												
3	859	NS	NS	S[5]	NS	330	241	78	259	0.807 (0.716, 0.874)	0.517 (0.472, 0.561)	Moderate
Index test 8: DLCN definite (score>8)												
4	1,088	NS	NS	VS[4]	NS	236	103	173	397	0.567 (0.460, 0.669)	0.802 (0.713, 0.869)	Low

1.*95%CI extend more than 15% in one direction for sensitivity and/or sensitivity, downgraded 1 level.*
2.Haralambos 2015 did not report n for those assessed by Simon Broome and undergoing genetic testing. Therefore n calculated on whole cohort.
3.95%CI extend more than 15% in each direction for both sensitivity and specificity, therefore downgraded 2 levels
4.I2 >75% for sensitivity and/or specificity, therefore very serious inconsistency (downgraded 2 levels)..
5.I2 >40% for sensitivity and/or specificity, therefore serious inconsistency (downgraded 1 level).

I.3 Management (statin monotherapy)

For high-intensity statin therapy in adults, please refer to CG181, section 11.3.1, table 41

Table 29: Management (Statin monotherapy) in children and young people: dichotomous outcomes

Quality assessment							No of patients		Effect estimate		Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment	Comparator	Relative (96% CI)	Absolute	
Outcome: Adverse events: 1 month											
2	RCT	No serious	No serious	very serious[2]	Serious[1]	none	83/184 (45.1%)	34/64 (53.1%)	0.86 [0.65, 1.13]	74 fewer per 1000 (from 186 fewer to 69 more)	Very low
Outcome: Adverse events: 6 months											
1	RCT	No serious	No serious	No serious	Serious[1]	none	88/140	29/47	1.02 [0.79, 1.32]	12 more per 1000 (from 130 fewer to 197 more)	Low
Outcome: change in aspartate aminotransferase concentration (x3 ULN)											
3	RCT	No serious	No serious	No serious	Very serious[3]	none	2/298 (0.67%)	2/172 (1.16%)	0.55 [0.08, 3.61]	5 fewer per 1000 (from 11 fewer to 30 more)	Low
Outcome: change in alanine aminotransferase concentration (x3 ULN)											
2	RCT	No serious	No serious	No serious	Very serious[3]	none	1/244 (0.41%)	0/154 (0%)	1.02 [0.04, 24.65]	n/a	Low
Outcome: change in CK concentration (x>10 ULN)											

Quality assessment							No of patients		Effect estimate		Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment	Comparator	Relative (96% CI)	Absolute	
2	RCT	No serious	No serious	No serious	Very serious[3]	none	4/167 (2.4%)	0/60 (0%)	3.23 [0.18, 58.84]	n/a	Low

1. *Confidence intervals: extend >25% in one direction, serious imprecision*
2. *Inconsistency very serious as I2=85%*
3. *Confidence intervals extend >25% in both directions, therefore very serious imprecision.*

Table 30: Management (statin monotherapy) in children and young people: continuous outcomes

Quality assessment							No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment (T)	Comparator (C)	Mean difference (95% CI)	
Outcome: Change in serum LDL cholesterol level (%) at end of follow up										
3	RCT	Serious[1]	No serious	Very serious[3]	Very serious[4]	none	297	172	-30.53 [-33.30, -27.77]	Very low
Outcome: Compliance (%): Rosuvastatin 5mg										
1	RCT	No serious	No serious	No serious	No serious	none	42	46	0.30 [-6.23, 6.83]	High
Outcome: Compliance (%) Rosuvastatin 10mg										
1	RCT	No serious	No serious	No serious	Serious[2]	none	44	46	3.40 [-2.72, 9.52]	Moderate
Outcome: Compliance (%): Rosuvastatin 20mg										
1	RCT	No serious	No serious	No serious	Serious[2]	none	45	46	2.50 [-3.80, 880]	Moderate

1.Allocation concealment not reported in Knipscheer 1996, McCrindle 2003 or Wiegman 2004
2. Confidence intervals more than 0.5 x SD in one direction and cross line of no difference, therefore serious imprecision..
3. I^2 94%, very serious inconsistency
4. Confidence intervals more than 0.5 x SD in both directions and cross line of no difference, therefore very serious imprecision..

Appendix J: Economic search strategy

J.1 Case finding

Databases that were searched, together with the number of articles retrieved from each database are shown in Table 31. The search strategy is shown in Table 32. The same strategy was translated for the other databases listed.

Table 31: Economic search summary

Economics	Date searched	Version/files	No. retrieved
MEDLINE (Ovid)	10/05/16	1946 to April Week 4 2016	446
MEDLINE in Process (Ovid)	10/05/16	May 09, 2016	50
Embase (Ovid)	10/05/16	1980 to 2016 Week 19	836
EconLit (Ovid)	10/05/16	1886 to March 2016	1
NHS Economic Evaluation Database (NHS EED) (legacy database)	10/05/16	Issue 2 of 4, April 2015	15
Health Technology Assessment (HTA Database)	10/05/16	Issue 2 of 4, April 2016	5
PubMed	10/05/16	N/A	23

Table 32: Economic search strategy

Database: Medline & Medline in Process
Search Strategy: --- 1 Hyperlipidemia, familial combined/ (728) 2 Hyperlipoproteinemia Type II/ (5602) 3 ((famil* or essential* or monogenic* or hereditar* or inherit* or heterozygous* or homozygous*) adj4 (hypercholest* or hyperlip* or cholest* or lipid* or FH)).tw. (12750) 4 (FH or HoFH or HeFH).tw. (5475) 5 Cholesterol, LDL/ or Receptors, LDL/ (30499) 6 (LDL* adj (cholester* or receptor* or lipoprotein*)).tw. (24823) 7 (low* adj1 densit* adj1 lipoprotein* adj1 (receptor* or cholesterol*)).tw. (22357) 8 (LDLR or LDL-R or LDL R or LDLC or LDL-C or LDL C).tw. (13872) 9 Apolipoprotein B-100/ (1746) 10 (Famili* adj2 apolipoprotein*).tw. (220) 11 ((Apolipoprotein* or Apo or Apo-) adj1 (B or B-100 or B100 or B 100) adj1 (deficien* or syndrom* or defectiv*)).tw. (240)

Database: Medline & Medline in Process

12 Hyperlipoproteinemia Type I/ or Apolipoprotein C-II/ (1093)

13 ((Apolipoprotein* or Apo or Apo-) adj1 (C or C-II or CII or C II or "C-2" or "C2" or "C 2") adj1 (deficien* or syndrom* or defectiv*)).tw. (21)

14 ((ApoC2 or ApoCII or ApoB) adj1 (deficien* or syndrom* or defectiv*)).tw. (66)

15 or/1-14 (73212)

16 Medical Records Systems, Computerized/ (18612)

17 Medical Records/ (63220)

18 Hospital Records/ (3197)

19 Databases, factual/ (52126)

20 Registries/ (62942)

21 Medical Audit/ (15642)

22 ((gp or general practi* or doctor* or nurse* or physician* or primary care or secondary care or clinic* or patient* or medical* or hospital* or computer* or electronic* or clinical practice*) adj2 (note* or record* or database* or regist* or audit* or data or datalink)).tw. (327937)

23 (GPRD or CPRD).tw. (453)

24 Medical History Taking/ or anamnes*.tw. (25534)

25 ((patient* or case* or medic*) adj2 (histor* or identif* or find* or screen*)).tw. (212440)

26 ((famil* or parent* or grand* or relative* or relation*) adj2 (histor* or case* or tracing or trace* or screen* or identif*)).tw. (83090)

27 (Simon adj1 Broom*).tw. (34)

28 (Dutch Lipid adj2 (clinic* or network* or criteria* or diagnos* or score*)).tw. (26)

29 DLCNCS.tw. (2)

30 Make Early Diagnosis to Prevent Early Death.tw. (9)

31 MEDPED.tw. (21)

32 ((cardiac* or coronar* or stroke or myocardial infarction or MI or heart attack) adj2 (care* or facili* or team* or unit* or investigat*) adj2 (note* or record* or database* or regist* or audit* or data)).tw. (223)

33 Myocardial Ischaemia National Audit Project.tw. (33)

34 MINAP.tw. (42)

Database: Medline & Medline in Process

35 National Institute for Cardiovascular Outcomes Research.tw. (14)

36 NICOR.tw. (10)

37 QRESEARCH.tw. (69)

38 National Audit of Percutaneous Coronary Intervention.tw. (1)

39 PCI.tw. (14392)

40 National Adult Cardiac Surgery.tw. (17)

41 NACSA.tw. (1)

42 Health Survey for England.tw. (340)

43 ((Patholog* or biochemistr* or lab or laborator*) adj2 (note* or record* or database* or regist* or audit* or data)).tw. (25961)

44 Genetic testing/ (29519)

45 ((cascade* or genetic*) adj2 (test* or train* or screen*)).tw. (24970)

46 ((selectiv* or proband* or proposit* or risk factor* or program*) adj2 (screen* or test*)).tw. (31888)

47 or/16-46 (864942)

48 15 and 47 (6236)

49 Economics/ (26697)

50 exp "Costs and Cost Analysis"/ (197191)

51 Economics, Dental/ (1878)

52 exp Economics, Hospital/ (21373)

53 exp Economics, Medical/ (13855)

54 Economics, Nursing/ (3934)

55 Economics, Pharmaceutical/ (2615)

56 Budgets/ (10427)

57 exp Models, Economic/ (11634)

58 Markov Chains/ (11182)

Database: Medline & Medline in Process

59 Monte Carlo Method/ (22517)

60 Decision Trees/ (9454)

61 econom$.tw. (175446)

62 cba.tw. (9050)

63 cea.tw. (17578)

64 cua.tw. (831)

65 markov$.tw. (13288)

66 (monte adj carlo).tw. (23357)

67 (decision adj3 (tree$ or analys$)).tw. (9409)

68 (cost or costs or costing$ or costly or costed).tw. (342963)

69 (price$ or pricing$).tw. (25523)

70 budget$.tw. (18907)

71 expenditure$.tw. (38325)

72 (value adj3 (money or monetary)).tw. (1513)

73 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (2979)

74 or/49-73 (720580)

75 "Quality of Life"/ (136462)

76 quality of life.tw. (158933)

77 "Value of Life"/ (5492)

78 Quality-Adjusted Life Years/ (8388)

79 quality adjusted life.tw. (7127)

80 (qaly$ or qald$ or qale$ or qtime$).tw. (5845)

81 disability adjusted life.tw. (1533)

82 daly$.tw. (1464)

83 Health Status Indicators/ (21241)

Database: Medline & Medline in Process

84 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (17078)

85 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1069)

86 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (3177)

87 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (22)

88 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (344)

89 (euroqol or euro qol or eq5d or eq 5d).tw. (4796)

90 (qol or hql or hqol or hrqol).tw. (28921)

91 (hye or hyes).tw. (54)

92 health$ year$ equivalent$.tw. (38)

93 utilit$.tw. (125903)

94 (hui or hui1 or hui2 or hui3).tw. (957)

95 disutili$.tw. (250)

96 rosser.tw. (72)

97 quality of wellbeing.tw. (6)

98 quality of well-being.tw. (340)

99 qwb.tw. (182)

100 willingness to pay.tw. (2665)

101 standard gamble$.tw. (683)

102 time trade off.tw. (803)

103 time tradeoff.tw. (215)

104 tto.tw. (658)

105 or/75-104 (359506)

106 74 or 105 (1030817)

107 48 and 106 (482)

Database: Medline & Medline in Process
108 Animals/ not Humans/ (4203766) 109 107 not 108 (482) 110 limit 109 to english language (446)

J.2 Diagnosis

Economics	Date searched	Version/files	No. retrieved
MEDLINE (Ovid)	07/10/16	1946 to September Week 4 2016	110
MEDLINE in Process (Ovid)	07/10/16	October 03, 2016	14
Embase (Ovid)	07/10/16		153
EconLit (Ovid)	07/10/16	1886 to September 2016	1
NHS Economic Evaluation Database (NHS EED) (legacy database)	07/10/16	Issue 2 of 4, April 2015	4
Health Technology Assessment (HTA Database)	07/10/16	Issue 3 of 4, July 2016	2
PubMed	07/10/16	n/a	6

Database: Medline & Medline in Process
Search Strategy: --- 1 Hyperlipidemia, familial combined/ (732) 2 Hyperlipoproteinemia Type II/ (5749) 3 ((famil* or essential* or monogenic* or hereditar* or inherit* or heterozygous* or homozygous*) adj4 (hypercholest* or hyperlip* or cholest* or lipid* or FH)).tw. (13192) 4 (FH or HoFH or HeFH).tw. (5742) 5 Cholesterol, LDL/ or Receptors, LDL/ (31538) 6 (LDL* adj (cholester* or receptor* or lipoprotein*)).tw. (25495) 7 (low* adj1 densit* adj1 lipoprotein* adj1 (receptor* or cholesterol*)).tw. (23397) 8 (LDLR or LDL-R or LDL R or LDLC or LDL-C or LDL C).tw. (14573) 9 Apolipoprotein B-100/ (1816) 10 (Famili* adj2 apolipoprotein*).tw. (220) 11 ((Apolipoprotein* or Apo or Apo-) adj1 (B or B-100 or B100 or B 100) adj1 (deficien* or syndrom* or defectiv*)).tw. (240) 12 Hyperlipoproteinemia Type I/ or Apolipoprotein C-II/ (1109) 13 ((Apolipoprotein* or Apo or Apo-) adj1 (C or C-II or CII or C II or "C-2" or "C2" or "C 2") adj1 (deficien* or syndrom* or defectiv*)).tw. (21) 14 ((ApoC2 or ApoCII or ApoB) adj1 (deficien* or syndrom* or defectiv*)).tw. (66) 15 or/1-14 (75847) 16 (Simon adj1 Broom*).tw. (36) 17 (Dutch Lipid adj2 (clinic* or network* or criteria* or diagnos* or score*)).tw. (33) 18 Dutch score*.tw. (4) 19 (DLCNCS or DLCN).tw. (10)

Database: Medline & Medline in Process

20 ((famil* or parent* or grand* or relative* or relation*) adj2 (histor* or case* or tracing or trace* or screen* or identif*) adj2 (famil* or essential* or monogenic* or hereditar* or inherit* or heterozygous* or homozygous*) adj4 (hypercholest* or hyperlip* or cholest* or lipid* or FH)).tw. (1503)

21 ((famil* or parent* or grand* or relative* or relation*) adj2 (histor* or case* or tracing or trace* or screen* or identif*) adj2 (coronar* or Ischaemic* or ischemic*) adj2 heart* adj2 (diseas* or disorder*)).tw. (324)

22 Genetic testing/ (30939)

23 ((cascade* or genetic* or dna) adj2 (test* or train* or screen*)).tw. (35227)

24 (tendon xanthomata or xanthelasmas).tw. (124)

25 ((corneal* or senil*) adj1 arcus).tw. (211)

26 or/16-25 (59196)

27 15 and 26 (2154)

28 Economics/ (26800)

29 exp "Costs and Cost Analysis"/ (203136)

30 Economics, Dental/ (1892)

31 exp Economics, Hospital/ (21897)

32 exp Economics, Medical/ (13976)

33 Economics, Nursing/ (3944)

34 Economics, Pharmaceutical/ (2654)

35 Budgets/ (10603)

36 exp Models, Economic/ (12134)

37 Markov Chains/ (11636)

38 Monte Carlo Method/ (23292)

39 Decision Trees/ (9741)

40 econom$.tw. (183183)

41 cba.tw. (9226)

42 cea.tw. (18056)

43 cua.tw. (850)

44 markov$.tw. (13949)

45 (monte adj carlo).tw. (24231)

46 (decision adj3 (tree$ or analys$)).tw. (9835)

47 (cost or costs or costing$ or costly or costed).tw. (359163)

48 (price$ or pricing$).tw. (26536)

49 budget$.tw. (19515)

50 expenditure$.tw. (39995)

51 (value adj3 (money or monetary)).tw. (1582)

52 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (3055)

53 or/28-52 (748730)

54 "Quality of Life"/ (144021)

55 quality of life.tw. (168881)

56 "Value of Life"/ (5527)

57 Quality-Adjusted Life Years/ (8879)

58 quality adjusted life.tw. (7630)

59 (qaly$ or qald$ or qale$ or qtime$).tw. (6223)

60 disability adjusted life.tw. (1665)

61 daly$.tw. (1575)

62 Health Status Indicators/ (21912)

63 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (18085)

64 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1100)

Database: Medline & Medline in Process
65 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (3449)
66 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (22)
67 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (350)
68 (euroqol or euro qol or eq5d or eq 5d).tw. (5281)
69 (qol or hql or hqol or hrqol).tw. (30826)
70 (hye or hyes).tw. (54)
71 health$ year$ equivalent$.tw. (38)
72 utilit$.tw. (132639)
73 (hui or hui1 or hui2 or hui3).tw. (1018)
74 disutili$.tw. (268)
75 rosser.tw. (72)
76 quality of wellbeing.tw. (8)
77 quality of well-being.tw. (354)
78 qwb.tw. (187)
79 willingness to pay.tw. (2859)
80 standard gamble$.tw. (705)
81 time trade off.tw. (849)
82 time tradeoff.tw. (217)
83 tto.tw. (694)
84 or/54-83 (379066)
85 53 or 84 (1075611)
86 27 and 85 (179)
87 Animals/ not Humans/ (4292287)
88 86 not 87 (179)
89 limit 88 to ed=20070101-20161007 (117)
90 limit 89 to english language (110)

J.3 Management (statin monotherapy)

Economics	Date searched	Version/files	No. retrieved
MEDLINE (Ovid)	07/10/16	1946 to September Week 4 2016	302
MEDLINE in Process (Ovid)	07/10/16	October 03, 2016	25
Embase (Ovid)	07/10/16		642
EconLit (Ovid)	07/10/16	1886 to September 2016	1
NHS Economic Evaluation Database (NHS EED) (legacy database)	07/10/16	Issue 2 of 4, April 2015	17
Health Technology Assessment (HTA Database)	07/10/16	Issue 3 of 4, July 2016	0
PubMed	07/10/16	n/a	1

Database: Medline & Medline in Process
Search Strategy:
---
1 Hyperlipidemia, familial combined/ (732)

Database: Medline & Medline in Process

2 Hyperlipoproteinemia Type II/ (5749)

3 ((famil* or essential* or monogenic* or hereditar* or inherit* or heterozygous* or homozygous*) adj4 (hypercholest* or hyperlip* or cholest* or lipid* or FH)).tw. (13192)

4 (FH or HoFH or HeFH).tw. (5742)

5 Cholesterol, LDL/ or Receptors, LDL/ (31538)

6 (LDL* adj (cholester* or receptor* or lipoprotein*)).tw. (25495)

7 (low* adj1 densit* adj1 lipoprotein* adj1 (receptor* or cholesterol*)).tw. (23397)

8 (LDLR or LDL-R or LDL R or LDLC or LDL-C or LDL C).tw. (14573)

9 Apolipoprotein B-100/ (1816)

10 (Famili* adj2 apolipoprotein*).tw. (220)

11 ((Apolipoprotein* or Apo or Apo-) adj1 (B or B-100 or B100 or B 100) adj1 (deficien* or syndrom* or defectiv*)).tw. (240)

12 Hyperlipoproteinemia Type I/ or Apolipoprotein C-II/ (1109)

13 ((Apolipoprotein* or Apo or Apo-) adj1 (C or C-II or CII or C II or "C-2" or "C2" or "C 2") adj1 (deficien* or syndrom* or defectiv*)).tw. (21)

14 ((ApoC2 or ApoCII or ApoB) adj1 (deficien* or syndrom* or defectiv*)).tw. (66)

15 or/1-14 (75847)

16 Atorvastatin Calcium/ (5553)

17 (Atorvastatin or Lipitor).tw. (6083)

18 Rosuvastatin Calcium/ (1964)

19 (Rosuvastatin or Crestor).tw. (2229)

20 Simvastatin/ or Ezetimibe, Simvastatin Drug Combination/ (6756)

21 (Simvador or Zocor or Inegy).tw. (112)

22 Pravastatin/ (3235)

23 (Statin* or Pravastatin).tw. (31429)

24 or/16-23 (38853)

25 15 and 24 (9271)

26 Economics/ (26800)

27 exp "Costs and Cost Analysis"/ (203136)

28 Economics, Dental/ (1892)

29 exp Economics, Hospital/ (21897)

30 exp Economics, Medical/ (13976)

31 Economics, Nursing/ (3944)

32 Economics, Pharmaceutical/ (2654)

33 Budgets/ (10603)

34 exp Models, Economic/ (12134)

35 Markov Chains/ (11636)

36 Monte Carlo Method/ (23292)

37 Decision Trees/ (9741)

38 econom$.tw. (183183)

39 cba.tw. (9226)

40 cea.tw. (18056)

41 cua.tw. (850)

42 markov$.tw. (13949)

43 (monte adj carlo).tw. (24231)

44 (decision adj3 (tree$ or analys$)).tw. (9835)

45 (cost or costs or costing$ or costly or costed).tw. (359163)

46 (price$ or pricing$).tw. (26536)

47 budget$.tw. (19515)

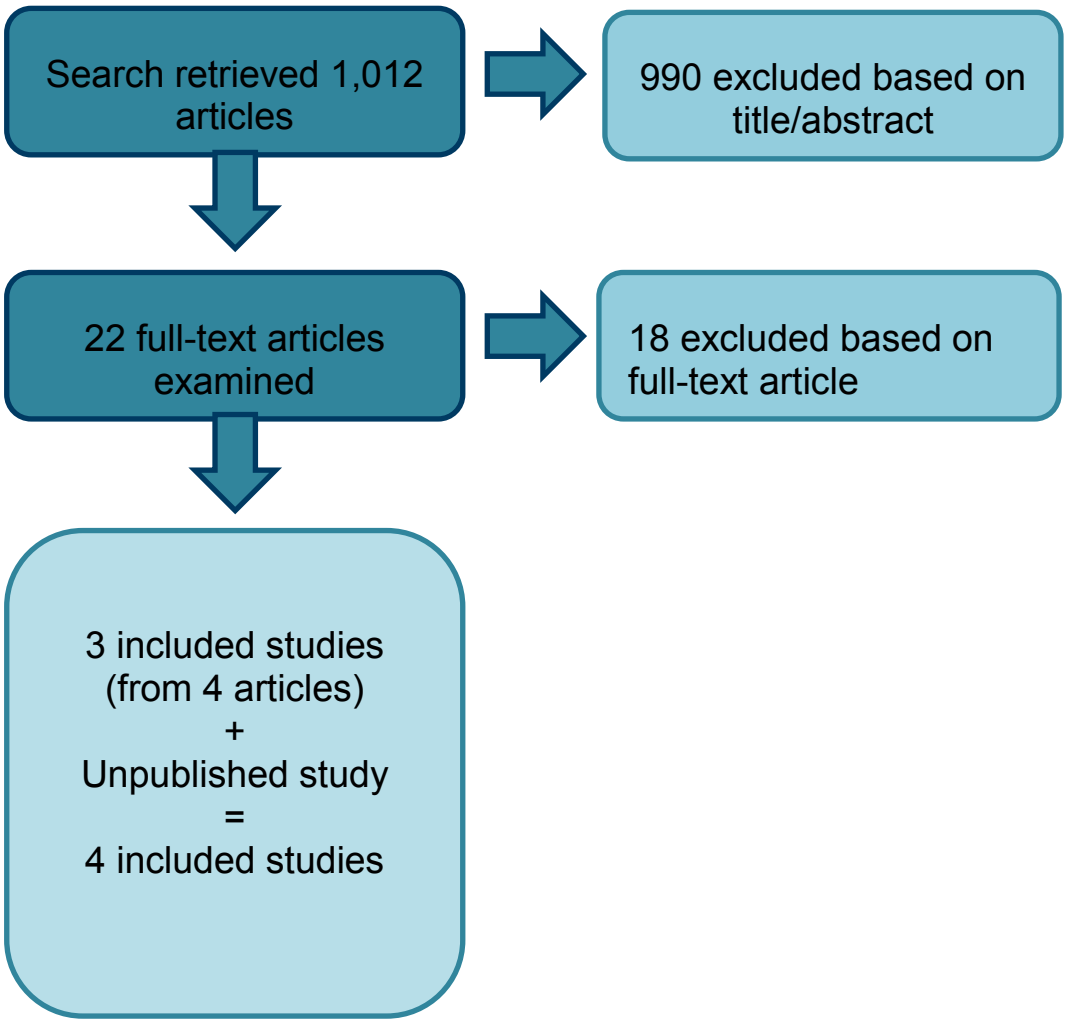
48 expenditure$.tw. (39995)

49 (value adj3 (money or monetary)).tw. (1582)

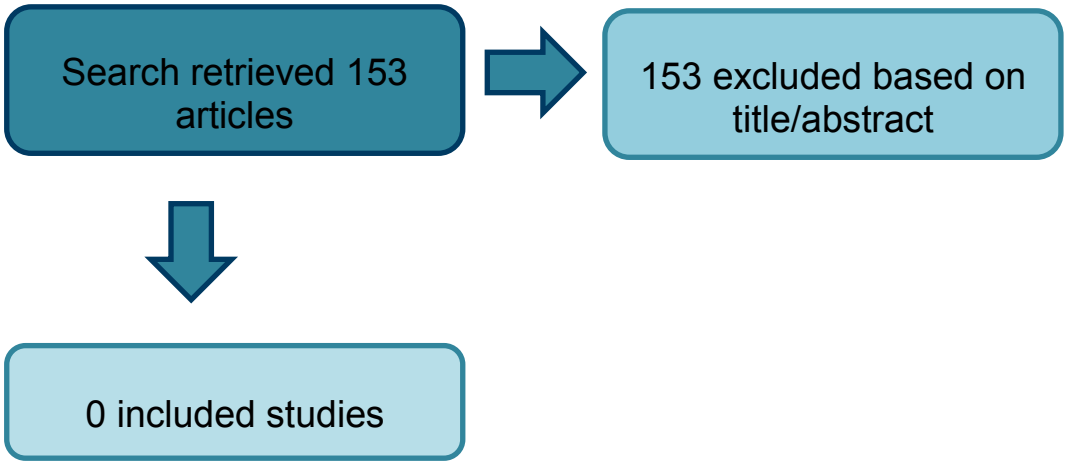
Database: Medline & Medline in Process
50 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (3055)
51 or/26-50 (748730)
52 "Quality of Life"/ (144021)
53 quality of life.tw. (168881)
54 "Value of Life"/ (5527)
55 Quality-Adjusted Life Years/ (8879)
56 quality adjusted life.tw. (7630)
57 (qaly$ or qald$ or qale$ or qtime$).tw. (6223)
58 disability adjusted life.tw. (1665)
59 daly$.tw. (1575)
60 Health Status Indicators/ (21912)
61 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (18085)
62 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1100)
63 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (3449)
64 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (22)
65 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (350)
66 (euroqol or euro qol or eq5d or eq 5d).tw. (5281)
67 (qol or hql or hqol or hrqol).tw. (30826)
68 (hye or hyes).tw. (54)
69 health$ year$ equivalent$.tw. (38)
70 utilit$.tw. (132639)
71 (hui or hui1 or hui2 or hui3).tw. (1018)
72 disutili$.tw. (268)
73 rosser.tw. (72)
74 quality of wellbeing.tw. (8)
75 quality of well-being.tw. (354)
76 qwb.tw. (187)
77 willingness to pay.tw. (2859)
78 standard gamble$.tw. (705)
79 time trade off.tw. (849)
80 time tradeoff.tw. (217)
81 tto.tw. (694)
82 or/52-81 (379066)
83 51 or 82 (1075611)
84 25 and 83 (596)
85 Animals/ not Humans/ (4292287)
86 84 not 85 (586)
87 limit 86 to ed=20070101-20161007 (327)
88 limit 87 to english language (302)

Appendix K: Economic review flowchart

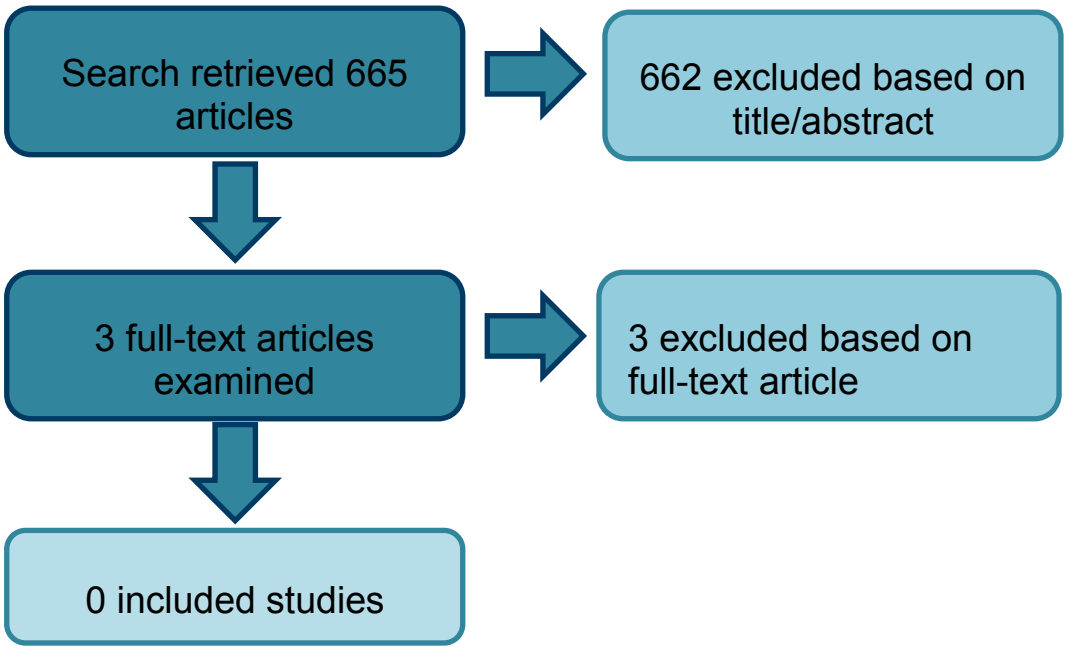
K.1 Case finding



K.2 Diagnosis



K.3 Management (statin monotherapy)



Appendix L:Economic excluded studies

The table below contains the full articles that were reviewed and excluded and the reasons for their exclusion.

L.1 Case finding

Table 33: Excluded economic studies (case finding)

Reference	Reason for exclusion
Ademi Z, Watts G F, Juniper A, and Liew D. (2013). A systematic review of economic evaluations of the detection and treatment of familial hypercholesterolemia. International Journal of Cardiology, 167, pp.2391-6.	Systematic review, checked against included and excluded studies
Antonanzas F, Rodriguez-Ibeas R, Hutter M F, Lorente R, Juarez C, and Pinillos M. (2012). Genetic testing in the European Union: does economic evaluation matter?. European Journal of Health Economics, 13, pp.651-61.	Systematic review, checked against included and excluded studies
Hadfield S G, and Humphries S E. ( ). Cascade testing is tried and tested and cost effective [1]. British Medical Journal, 335, pp..	Narrative review
Fox K F. (1892). Familial hypercholesterolaemia -Screening is effective, but is it cost effective?. European Heart Journal, 23, pp.1892-1893.	Narrative review
Hadfield G S, and Humphries S E. (2007). Familial hypercholesterolaemia: Cascade testing is tried and tested and cost effective. BMJ, 335, pp.683.	Narrative review
Parrella A, Mundy L, and Hiller J E. (2007). Genetic screening for Familial Hypercholesterolaemia (Structured abstract). Health Technology Assessment Database, , pp..	Narrative review
Pears R, Griffin M, Futema M, and Humphries S E. (2015). Improving the cost-effectiveness equation of cascade testing for familial hypercholesterolaemia. Current Opinion in Lipidology, 26, pp.162-8.	Narrative review
Hadfield S G, Horara S, Starr B J, Yazdgerdi S, Marks D, Bhatnagar D, Cramb R, Egan S, Everdell R, Ferns G, Jones A, Marenah C B, Marples J, Prinsloo P, Sneyd A, Stewart M F, Sandle L, Wang T, Watson M S, Humphries S E, Steering Group for the Department of Health Familial Hypercholest, and Project . (2009). Family tracing to identify patients with familial hypercholesterolaemia: the second audit of the Department of Health Familial Hypercholesterolaemia Cascade Testing Project. Annals of Clinical Biochemistry, 46, pp.24-32.	Cost analysis only, selectively excluded because other included studies included health benefits
Pears R, Griffin M, Watson M, Wheeler R, Hilder D, Meeson B, Bacon S, and Byrne CD. (2014). The reduced cost of providing a nationally recognised service for familial hypercholesterolaemia. BMJ, 1, pp.e000015.	Cost analysis only, selectively excluded because other included studies included health benefits
Atienza G. (2006). Familial hypercholesterolemia: evaluation of genetic screening by DNA microarrays (Structured abstract). Health Technology Assessment Database, , pp..	Could not obtain
Anonymous . ( ). Family tracing most cost-effective way of detecting high cholesterol. Pharmaceutical Journal, 268, pp..	Could not obtain
Oliva J, Lopez-Bastida J, Moreno S G, Mata P, and Alonso R. (2009). Cost-effectiveness analysis of a genetic screening program in the close relatives of Spanish patients with familial hypercholesterolemia (Structured abstract). Revista Espanola de Cardiologia, 62, pp.57-65.	Could not obtain

Reference	Reason for exclusion
Marang-van de Mheen, P J, Asbroek A H, Bonneux L, Bonsel G J, and Klazinga N S. (2002). Cost-effectiveness of a family and DNA based screening programme on familial hypercholesterolaemia in The Netherlands (Structured abstract). European Heart Journal, 23, pp.1922-1930.	Classified as not applicable by the quality assessment checklist for economic studies
Marks D, Wonderling D, Thorogood M, Lambert H, Humphries S E, and Neil H A. (2000). Screening for hypercholesterolaemia versus case finding for familial hypercholesterolaemia: a systematic review and cost-effectiveness analysis. Health Technology Assessment (Winchester, and England), 4, pp.1-123.	This study is over 15 years old and the methods used to diagnose FH, treat FH and conduct economic anslysis have changed
Marks D, Wonderling D, Thorogood M, Lambert H, Humphries S E, and Neil H A. (2002). Cost effectiveness analysis of different approaches of screening for familial hypercholesterolaemia. BMJ, 324, pp.1303.	(journal article version of Marks et al 2000) This study is over 15 years old and the methods used to diagnose FH, treat FH and conduct economic anslysis have changed
Marks D, Thorogood M, Neil H A, Wonderling D, and Humphries S E. (2003). Comparing costs and benefits over a 10 year period of strategies for familial hypercholesterolaemia screening. Journal of Public Health Medicine, 25, pp.47-52.	Population screening
Sharma P, Boyers D, Boachie C, Stewart F, Miedzybrodzka Z, Simpson W, Kilonzo M, McNamee P, and Mowatt G. (2012). Elucigene FH20 and LIPOchip for the diagnosis of familial hypercholesterolaemia: a systematic review and economic evaluation. Health Technology Assessment (Winchester, and England), 16, pp.1-266.	These technologies are no longer commercially available following this HTA conducted for NICE diagnostics guidance 2
Wonderling D, Umans-Eckenhausen M A, Marks D, Defesche J C, Kastelein J J, and Thorogood M. (2004). Cost-effectiveness analysis of the genetic screening program for familial hypercholesterolemia in The Netherlands. Seminars in Vascular Medicine, 4, pp.97-104.	Classified as not applicable by the quality assessment checklist for economic studies

L.2 Diagnosis

Not applicable

L.3 Management (statin monotherapy)

Table 34: Excluded economic studies (management (statin monotherapy))

Reference	Reason for exclusion
Watts GF, Juniper A, van Bockxmeer F, Ademi Z, Liew D, O'Leary P. (2012). Familial hypercholesterolaemia: a review with emphasis on evidence for treatment, new models of care and health economic evaluations. International Journal of Evidence-Based Healthcare, 10: 211-221	Narrative review only
Nherera L, Calvert NW, DeMott K, Humphries S, Neil HAW, Minhas R, Thorogood M. (2010). Cost-effectiveness analysis of the use of a high-intensity statin compared to a low-intensity statin in the management of patients with familial hypercholesterolaemia	Inappropriate comparator, review protocol specifies placebo only
Ademi Z, Watts GF, Juniper A, Liew D. (2013). A systematic review of economic evaluations of the detection and treatment of familial hypercholesterolaemia. International Journal of Cardiology, 167: 2391-2396	Systematic review, included studies checked against present included/excluded studies.

Appendix M: Full economic evidence tables

These are the full evidence tables for all included economic studies.

Table 35: Full economic evidence tables

Bibliographic reference	Kerr et al M, Pears R, Miedzybrodzka Z, Haralambos K, Cather M, Watson M, Humphries S. (2017). Cost effectiveness of cascade testing for familial hypercholesterolaemia, based on data from FH services in the UK.

Overview

Interventions	Genetic cascade testing from index cases with a monogenic mutation
Comparators	No cascade testing
Population	People with monogenic FH
Type of Analysis	Cost-utility analysis
Structure	Decision tree and Markov model
Cycle length	1 year
Time horizon	Lifetime
Perspective	NHS and PSS
Country	UK
Currency unit	£
Cost year	2015
Discounting	3.5%
Other comments	This is an unpublished analysis provided by one of the topic experts. Methods and results considered by the committee may differ from those used in the final published version.

Results

Strategy	Cost	Effect	Incremental cost	Incremental effect	ICER
No cascade testing	Incremental results only reported		-	-	-
Genetic cascade testing			£2,781	0.48	£5,981/QALY

<table>
<tr><td>Bibliographic reference</td><td>Kerr et al M, Pears R, Miedzybrodzka Z, Haralambos K, Cather M, Watson M, Humphries S. (2017). Cost effectiveness of cascade testing for familial hypercholesterolaemia, based on data from FH services in the UK.</td></tr>
<tr><td>Data sources</td><td>
<table>
<tr><td>Base-line data</td><td>• Risk of cardiovascular events from QRISK2 as per lipid modification guideline adjusted for FH-specific uplift from Simon Broome register</td></tr>
<tr><td>Effectiveness data</td><td>• Cholesterol Treatment Trialists Collaborators study</td></tr>
<tr><td>Cost data</td><td>• UK genetic testing service for genetic testing
• Resource use from Welsh, Scottish and Wessex services
• Reference costs from Personal and Social Services Research Unit</td></tr>
<tr><td>Utility data</td><td>• As per lipid modification guideline CG181</td></tr>
</table>
</td></tr>
<tr><td>Uncertainty</td><td>
<table>
<tr><td>One-way sensitivity analysis</td><td>• Increased LDL-C reduction from 37% to 50%: ICER range £3,527 to £8,398 according to age band
• Increased number of relatives approached to 6: ICER range from £2,227 to £3,785 according to age band
• Reduce compliance to 70%: ICER range from £5,877 to £13,551 according to age band
• Reduce cost of rosuvastatin and ezetimibe: ICER range £3,174 to £9,089</td></tr>
<tr><td>Probabilistic sensitivity analysis</td><td>Not conducted</td></tr>
</table>
</td></tr>
<tr><td>Applicability</td><td>Partially Applicable

• Case identification strategies not included</td></tr>
<tr><td>Limitations</td><td>Minor limitations

• No probabilistic sensitivity analysis
• Unclear how administration and staff costs supporting genetic testing were calculated
• Unclear how gender is accounted for in the model (the lipid modification Markov model calculates cost effective separately for males and females)</td></tr>
<tr><td>Conflicts</td><td>Funded by Heart UK</td></tr>
</table>

Bibliographic reference	**Ademi Z, Watts G F, Pang J, Sijbrands E J, van Bockxmeer , F M, O'Leary P, Geelhoed E, and Liew D. (2014). Cascade screening based on genetic testing is cost-effective: evidence for the implementation of models of care for familial hypercholesterolemia. Journal of Clinical Lipidology, 8, pp.390-400.**

Overview

Interventions	Nurse-led cascade screening for FH using primarily genetic testing supplemented with the measurement of LDL-C, followed by treatment with statins
Comparators	No cascade screening
Population	Relatives of index cases (first and second degree relatives), start age 42 years of age
Type of Analysis	Cost-utility analysis
Structure	Decision tree and Markov model
Cycle length	1 year
Time horizon	10 years
Perspective	Australian public health care system
Country	Australia
Currency unit	Australian dollars
Cost year	2013
Discounting	5% costs and benefits, 3% in sensitivity analysis
Other comments	3 health states for Markov model • Alive without CHD • Alive with CHD • Alive Dead Assumed relatives tested and found to be negative for FH received no further follow up or change in management of health so that downstream health and cost outcomes were identical between screening and no screening groups Assumed annual risk of death from non-CHD causes for general population was the same as that for FH patients without CHD Assumed all people identified as having FH would be started on atorvastatin at a weighted-average dose of 60mg daily Compliance with statin treatment assumed to be 100% Software used: Excel with @Risk for probabilistic analysis

Bibliographic reference	**Ademi Z, Watts G F, Pang J, Sijbrands E J, van Bockxmeer , F M, O'Leary P, Geelhoed E, and Liew D. (2014). Cascade screening based on genetic testing is cost-effective: evidence for the implementation of models of care for familial hypercholesterolemia. Journal of Clinical Lipidology, 8, pp.390-400.**

Results

Strategy	Cost	Effect	Incremental cost	Incremental effect	ICER
No cascade screening	AUD$7,048	7.52 QALYs	-	-	-
Cascade screening	AUD$8,084	7.81 QALYs	AUD$1,036	0.29	AUD$3,565/QALY ($2,004 to $5,228) or £1,749.25 (2016)

Data sources

Base-line data	• Demographic information and clinical characteristics of 81 index cases and 175 adult relatives from the author's own centre • Prevalence of FH assumed to be 54.3% based on DNA testing alone • 11.9% per person per year probability of fatal and non-fatal CHD from Dutch cohort, 34.2% of this fatal, from published Western Australia study • Death from non-CHD causes from 2007 Australian life tables • Proportion of people newly identified with FH already taking cholesterol-lowering therapy 46.3% based on author's own service (same for no cascade screen comparator)
Effectiveness data	• DNA testing 100% sensitivity and 100% specificity based on published studies on the author's testing service • Relative risk of treatment with atorvastatin taken from Dutch cohort (0.24, 95% CI 0.18 to 0.30)

Cost data	• Cost of testing AUD$1,005 per relative based on author's own centre
	• Cost of confirmation DNA test for index case, AUD$506 based on author's own centre
	• Cost of all post-screening test for those identified with FH AUD$128 and annual clinic visits AUD$216 from Australian Medical Benefit Schedule
	• Cost of atorvastatin based on Australian Pharmaceutical Benefits Scheme and assumed 50% on 40mg and 50% on 80mg resulting in an average cost of AUD$759 annually
	• Cost of incident CHD (1 event only) based on Australian Refined Diagnosis Related Groups
	  ○ Nonfatal MI AUD$8,606
	  ○ Fatal MI AUD$6,590
	• Ongoing cost of CHD AUD$4,879 based on published study and indexed

Bibliographic reference	**Ademi Z, Watts G F, Pang J, Sijbrands E J, van Bockxmeer , F M, O'Leary P, Geelhoed E, and Liew D. (2014). Cascade screening based on genetic testing is cost-effective: evidence for the implementation of models of care for familial hypercholesterolemia. Journal of Clinical Lipidology, 8, pp.390-400.**
	Utility data: • From published studies: 1 for alive without CHD; 0.9 (95% CI 0.81 to 1) for alive with CHD
Uncertainty	**One-way sensitivity analysis**: ICERs most sensitive to annual risk of CHD and relative benefit of statins • RR prevention nonfatal myocardial infarction 0.85: AUD$12,626/QALY • RR prevention cardiovascular death: 0.87: AUD$16,880/QALY All one-way sensitivity analysis remains below AUD$17,000/QALY Additional analysis based on age-and gender-adjusted LDL-C threshold for diagnosis of close relatives with FH for cascade screening was observed as a cost-effective strategy compared with no screening with an ICER of AUD$3,287/QALY. The yield of FH relatives detected from index cases was comparable to genetic testing (1.09 to 1.17) with incrementally less costs because the cost of the DNA test can be removed. **Probabilistic sensitivity analysis**: 99% probability cascade screening was below AUD$50,000 per QALY threshold
Applicability	**Partially Applicable** • Based on the Australian health care system – although the general model of care is probably similar to cascade testing services offered in the UK, costs may not be representative of those incurred by the NHS. • The analysis focussed on the cost effectiveness of cascade screening only. The current update is also interested in the identification of index cases by searching databases. • Side effects of statin treatment not included. There may be additional events other than coronary heart disease that can be prevented by diagnosing FH and offering lipid modification. • 5% discount rate used in base case, although 3% was used in a sensitivity analysis (3.5% is NICE's reference case) • QALYs are used to represent health outcomes but it is unknown whether they were based on the EQ-5D

Bibliographic reference	**Ademi Z, Watts G F, Pang J, Sijbrands E J, van Bockxmeer , F M, O'Leary P, Geelhoed E, and Liew D. (2014). Cascade screening based on genetic testing is cost-effective: evidence for the implementation of models of care for familial hypercholesterolemia. Journal of Clinical Lipidology, 8, pp.390-400.**
Limitations	**Potentially serious limitations** • Only 3 health states were used in the Markov model to represent patients with or without coronary heart disease. This may be an oversimplification of the events that could be avoided by diagnosing FH and providing lipid-modifying treatment. • Triangular distributions used for relative risk of fatal and nonfatal CHD events. Lognormal is preferred for this type of parameter. The choice to use a triangular distribution may have made the intervention more cost effective than it otherwise would have been to the extent that a lognormal distribution would have allowed less effective relative risks greater than the upper range of the triangular distribution, 0.3. • Uniform distribution used for costs. Gamma or lognormal distributions are preferred for this type of parameter. It is difficult to predict whether this would have favoured the intervention or comparator. • Age-dependent population norms for utilities not used • The additional analysis of LDL-C thresholds was not included as a discrete intervention in incremental analysis with the main results. Assuming this is a mutually exclusive option and is slightly less effective with less costs than the DNA testing strategy, the cost effectiveness of the DNA testing strategy should be calculated by comparing it against the LDL-C threshold category, not no cascade screening. Insufficient information was provided for the update analyst to conduct incremental analysis. • The time horizon is 10 years rather than lifetime specified in the reference case. • Diagnostic yield of testing programme based on author's own centre experience of 81 index cases without cross-checking with published literature. • Scant details are provided on the resource use calculations adopted to calculate the cost of cascade screening.
Conflicts	Author's FH programme funded by Australia Better Health Initiative and the Department of Health of Western Australia

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; CHD: coronary heart disease; FH: familial hypercholesterolaemia

Bibliographic reference	Chen C X, and Hay J W. (2015). Cost-effectiveness analysis of alternative screening and treatment strategies for heterozygous familial hypercholesterolemia in the United States. International Journal of Cardiology, 181, pp.417-24.

Overview

Interventions	• Genetic cascade screening of at-risk relatives • Enhanced lipid cascade screening and statin adherence programme
Comparators	Lipid cascade screening
Population	Caucasian male adults with a family history of FH and high-risk baseline cholesterol levels of 46 mg/dL HDL-C, 224 mg/dL LDL-C and 305 total cholesterol
Type of Analysis	Cost-utility analysis
Structure	Decision tree and Markov model
Cycle length	1 year
Time horizon	Lifetime
Perspective	US societal
Country	United States
Currency unit	US$
Cost year	2013
Discounting	3%
Other comments	Software: Excel Assume that people with a negative genetic test still receive statin therapy if they have high LDL-C. 3 health states in Markov: • Pre-CVD • CVD event/stroke • Death Treatment based on 10mg atorvastatin Adherence decreases with time across all arms except for the intervention arm enhanced lipid cascade screening and statin adherence.

Bibliographic reference	**Chen C X, and Hay J W. (2015). Cost-effectiveness analysis of alternative screening and treatment strategies for heterozygous familial hypercholesterolemia in the United States. International Journal of Cardiology, 181, pp.417-24.**

Results

Strategy	Cost	Effect	Incremental cost	Incremental effect	ICER
Lipid cascade screening	$10,396	18.28	-	-	-
Genetic cascade screening	$15,594	18.29	$5,198	0.01	Extendedly dominated
Lipid cascade screening and adherence programme	$16,385	18.77	$5,989	0.49	US$12,223/QALY (£8,845 (2016))

If the lipid cascade screening and adherence programme is excluded from this analysis because it is deemed to be irrelevant to the update, genetic cascade screening had an ICER of US$519,813 per QALY, not cost effective compared with lipid cascade screening.

Data sources

Base-line data	Baseline progression from Simon Broome Register Transition probabilities of CVD and CVD death from Framingham heart study Hazard ratio of death after CVD event or stroke: 5 Baseline adherence (year 1-9 of therapy): 56% Baseline adherence (year 10 onwards): 52%
Effectiveness data	From peer-reviewed literature Sensitivity of DNA testing 78.5% Increase in adherence with adherence programme: 38% Decrease in total cholesterol due to statin therapy: 28% Decrease in LDL cholesterol due to statin therapy: 38%
Cost data	From peer-reviewed literature First year screen costs: • Lipid screening US$334 • Lipid screen and adherence programme: US$334 • Genetic screening US$5528 Cholesterol testing for FH cases every 2 years • Lipid screening US$233 • Lipid screen and adherence programme: US$233 • Genetic screening US$233

Bibliographic reference	**Chen C X, and Hay J W. (2015). Cost-effectiveness analysis of alternative screening and treatment strategies for heterozygous familial hypercholesterolemia in the United States. International Journal of Cardiology, 181, pp.417-24.**

	Annual statin treatment costs • Lipid screening US$106 • Lipid screen and adherence programme: US$352 • Genetic screening US$106
Utility data	From peer-reviewed literature Disutility in the pre-CVD state to reflect the act of taking a daily statin prescription with mild side effects 0.004 US population norms from the literature to adjust age-based utility CVD event/stroke state: 0.68

Uncertainty

One-way sensitivity analysis	Only FH gene sequencing and DNA testing costs had a large effect on the ICER results between genetic cascade screening and lipid cascade screening, although the ICER remained above $150,000 per QALY. All other parameters only produced changes in this ICER less than 1%. Threshold analysis found that genetic cascade screening became cost effective at a threshold of $150,000 per QALY when the first year screening cost was less than $1,830 per person.
Probabilistic sensitivity analysis	99% probability that lipid screening plus adherence programme is cost effective compared with lipid cascade screening 55% probability that genetic cascade screening is cost effective compared with lipid cascade screening at a threshold of $150,000/QALY

Applicability

Partially Applicable

- The modelled cohort is based on males only
- It is likely the costs of the US health care system do not represent those incurred by the NHS. The first year screening cost of US$5,528 far exceeds what would be incurred by the NHS. A sensitivity analysis found that genetic cascade screening was cost effective compared with lipid cascade screening for a first year screening cost of $1,830 and it is likely that the cost in the UK is less than this.
- The 10mg dose of atorvastatin is less than the high potency treatment recommended by UK guidelines.

Bibliographic reference	**Chen C X, and Hay J W. (2015). Cost-effectiveness analysis of alternative screening and treatment strategies for heterozygous familial hypercholesterolemia in the United States. International Journal of Cardiology, 181, pp.417-24.**
Limitations	**Potentially serious limitations** • The Markov model based on 3 health states may oversimplify the health states relevant to the risks that lipid-modification hopes to address • Inappropriate distributions used. Normal distributions used for transition probabilities and utilities. Triangle distributions used for hazard ratio of death after CVD event and disutility from statin medication in the pre-CVD state.
Conflicts	The authors report no relationship that could be construed as a conflict of interest.

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; CVD: cardiovascular disease; FH: familial hypercholesterolaemia

Bibliographic reference	**National Collaborating Centre for Primary Care. (2008). Familial Hypercholesterolaemia, appendix E, health economic modelling. , NICE Clinical Guideline 71, pp..** **Nherera L, Marks D, Minhas R, Thorogood M, and Humphries S E. (2011). Probabilistic cost-effectiveness analysis of cascade screening for familial hypercholesterolaemia using alternative diagnostic and identification strategies. Heart, 97, pp.1175-1181.**
Overview	

Interventions	1.Cholesterol method – relatives diagnosed based on elevated LDL-C levels 2.DNA method – only people with an identified FH-causing mutation were included for cascade testing, with the relatives tested for the family mutation, and secondary cascading for those with the family mutation 3.DNA+DFH method – As per 2. DNA method, and in addition, in the relatives of definite familial hypercholesterolaemia index cases where no mutation can be found, cascade testing was undertaken using measures of LDL-C levels to identify affected relatives for treatments and for secondary cascading 4.DNA+DFH+PFH method – As per 2. DNA method, and in addition, cascade testing is undertaken in both definite familial hypercholesterolaemia and probable familial hypercholesterolaemia index cases using LCL-C measures.
Population	Relatives of people with FH
Type of Analysis	Cost-utility analysis
Structure	Decision tree and Markov model
Cycle length	1 year
Time horizon	Lifetime
Perspective	NHS

Bibliographic reference	**National Collaborating Centre for Primary Care. (2008). Familial Hypercholesterolaemia, appendix E, health economic modelling. , NICE Clinical Guideline 71, pp..** **Nherera L, Marks D, Minhas R, Thorogood M, and Humphries S E. (2011). Probabilistic cost-effectiveness analysis of cascade screening for familial hypercholesterolaemia using alternative diagnostic and identification strategies. Heart, 97, pp.1175-1181.**

Country	United Kingdom
Currency unit	£
Cost year	2007
Discounting	3.5%
Other comments	All index cases with a positive diagnosis of FH were offered high intensity statin treatment. In all strategies, all relatives identified with elevated LDL-C were offered lipid-lowering therapies (high intensity statins for mutation carriers and low intensity statins if they do not carry the family mutation). Assumed uptake of cascade testing 65% for first degree relatives and 60% for second degree relatives Assumed every index case had 5 first degree relatives, each of these five has two first degree relatives, and each of these has two first degree relatives. 8 states for Markov: • Well • Unstable angina • Myocardial infarction • PAD stroke • Heart failure • Revascularisation • Cardiovascular death • Death from other causes

Results

Deterministic results reported by NCCPC 2008

Strategy	Cost	Effect	Incremental cost	Incremental effect	ICER (£/QALY)
Cholesterol	£38,921	32.87	-	-	-
DNA	£44,816	30.63	-	-	Dominated
DNA+DFH	£46,479	31.91	-	-	Dominated
DNA+DFH+PFH	£51,924	37.73	£13,003	4.86	£2,676

Probabilistic results reported by Nherera et al. 2011

Strategy	Cost	Effect	Incremental cost	Incremental effect	ICER (£/QALY)
Cholesterol	£44,576	10.89	-	-	-

Bibliographic reference	**National Collaborating Centre for Primary Care. (2008). Familial Hypercholesterolaemia, appendix E, health economic modelling. , NICE Clinical Guideline 71, pp..** **Nherera L, Marks D, Minhas R, Thorogood M, and Humphries S E. (2011). Probabilistic cost-effectiveness analysis of cascade screening for familial hypercholesterolaemia using alternative diagnostic and identification strategies. Heart, 97, pp.1175-1181.**

DNA	£50,918	24.12	£6,341	13.23	£479
DNA+DFH	£52,670	24.28	-	-	Extendedly dominated
DNA+DFH+PFH	£54,799	25.18	£3,881	1.06	£3,666

Data sources

Base-line data	Relative risk of CVD due to FH from Simon Broome database For relatives who have elevated LDL-C but no FH their risk was assumed to be 20% more than the general population. Based on UK FH audit 30% definite FH and 60% probable FH
Effectiveness data	Cholesterol method • assumed that 90% of the definite FH and 35% of the probable FH had true FH; and 10% definite FH and 65% probable FH were false positive. For relatives, this was combined with published data on identification rates, true positive 32%, False positive 8%, true negative 42%, false negative 18% DNA method • Mutation detection rate in definite FH 80%, 50% in relatives • True positives 90% of definite FH; false negatives 7% of probable FH DNA+DFH method Additional testing using LDL-C diagnostic cutoffs in all 60/1000 no-mutation definite FH people of whom 50% were true positive and 50% false positive. DNA+DFH+PFH method Additional LDL-C testing on 420/1000 non-mutation PFH index cases of whom 7% are true positive and 93% false positive
Cost data	Treatment cost from Prescription Pricing Division Staff cost from PSSRU unit costs Time taken from FH audit report Cost of CVD events from TA94
Utility data	From literature

<table>
<tr><td>Bibliographic reference</td><td>National Collaborating Centre for Primary Care. (2008). Familial Hypercholesterolaemia, appendix E, health economic modelling. , NICE Clinical Guideline 71, pp..
Nherera L, Marks D, Minhas R, Thorogood M, and Humphries S E. (2011). Probabilistic cost-effectiveness analysis of cascade screening for familial hypercholesterolaemia using alternative diagnostic and identification strategies. Heart, 97, pp.1175-1181.</td></tr>
<tr><td>Uncertainty</td><td>
<table>
<tr><td>One-way sensitivity analysis</td><td>Increase starting age to 65 (from 50) for index cases and 45 (from 30) for relatives: ICER reduced to £2,000/QALY
Treatment effect using upper and lower 95% confidence interval of IDEAL and TNT trials: ICER stays below £3,000/QALY
Treatment cost increased by £100 per year: ICER increases to £2,811/QALY
Doubling and halving time and cost of staff time for cascade testing: ICERs stay around £3,000/QALY for DNA+DFH+PFH vs. cholesterol method
Change in relatives per index case does not change ICER much
Increased uptake rate to 85% for index cases (from 65%) and 80% for relatives (from 60%) and ICER fell. However, a decrease in uptake rate was not tested
Reducing price of statin treatment reduced ICER to £2,509/QALY</td></tr>
<tr><td>Probabilistic sensitivity analysis</td><td>Conducted in Nherera et al. 2011, found that DNA+DFH+PFH has a 100% probability of being cost effective compared with the cholesterol method.</td></tr>
</table>
</td></tr>
<tr><td>Applicability</td><td>Partially applicable</td></tr>
<tr><td>Limitations</td><td>Potentially serious limitations

• The diagnostic definitions change according to strategy. For example, a true positive can have elevated LDL-C levels or be a carrier of the family mutation. That is, a person with a family mutation would be a true positive in a DNA strategy but not in the cholesterol strategy if they do not have raised cholesterol. Therefore, the results are not necessarily comparable between strategies.
•</td></tr>
<tr><td>Conflicts</td><td>As per declarations of interest in full guideline</td></tr>
</table>

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; DNA: Deoxyribonucleic acid; FH: familial hypercholesterolaemia; DFH: definite familial hypercholesterolaemia as defined by the Simon Broome criteria; PFH: possible familial hypercholesterolaemia as defined by the Simon Broome criteria

Appendix N: Quality assessment checklists for economic studies

These are the quality assessment checklists for included economic studies.

Table 36: Quality assessment checklists for economic studies

Section 1: Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5) This checklist should be used first to filter out irrelevant studies.	**Yes/partly/no/unclear/ NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	
1.2 Are the interventions appropriate for the review question?	Partly	No case identification strategies
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	Yes	
1.5 Are all direct effects on individuals included, and are all other effects included where they are material?	Yes	
1.6 Are all future costs and outcomes discounted appropriately?	Yes	
1.7 Is QALY used as an outcome, and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	Yes	
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	n/a	
1.9 **Overall judgement:** Partially applicable There is no need to use section 2 of the checklist if the study is considered 'not applicable'.		
Other comments:		
Section 2: Study limitations (the level of methodological quality) This checklist should be used once it has been decided that the study is sufficiently applicable to the context of the guideline	**Yes/partly/no/unclear/ NA**	**Comments**
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	
2.3 Are all important and relevant outcomes included?	Yes	
2.4 Are the estimates of baseline outcomes from the best available source?	Partly	The relative risk of non-fatal cardiovascular events for the FH

		population are based on the increased risk of mortality reported by the Simon Broome register.
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	
2.6 Are all important and relevant costs included?	Yes	
2.7 Are the estimates of resource use from the best available source?	Yes	Unclear how administration and staff costs around genetic testing were calculated.
2.8 Are the unit costs of resources from the best available source?	Yes	
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	
2.11 Is there any potential conflict of interest?	Yes	Funded by patient advocacy group
2.12 **Overall assessment:** Minor limitations		
Other comments: No probabilistic sensitivity analysis Unclear how gender was accounted for considering the lipid modification model calculates results separately for males and females.		

Ademi Z, Watts G F, Pang J, Sijbrands E J, van Bockxmeer , F M, O'Leary P, Geelhoed E, and Liew D. (2014). Cascade screening based on genetic testing is cost-effective: evidence for the implementation of models of care for familial hypercholesterolemia. Journal of Clinical Lipidology, 8, pp.390-400.		
Section 1: Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5) This checklist should be used first to filter out irrelevant studies.	**Yes/partly/no/unclear/ NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	
1.2 Are the interventions appropriate for the review question?	Partly	Apart from cascade testing, the update is also interested in index case identification through database searching
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	The study is based on the Australian health care system. The model of care sounded generally similar to what occurs in the UK but some of the costs may not represent those incurred by the NHS.
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	Yes	
1.5 Are all direct effects on individuals included, and are all other effects included where they are material?	Partly	The side effects of statins are not included. There may additional events other than coronary heart

Ademi Z, Watts G F, Pang J, Sijbrands E J, van Bockxmeer , F M, O'Leary P, Geelhoed E, and Liew D. (2014). Cascade screening based on genetic testing is cost-effective: evidence for the implementation of models of care for familial hypercholesterolemia. Journal of Clinical Lipidology, 8, pp.390-400.		
		disease that are prevented by identifying FH.
1.6 Are all future costs and outcomes discounted appropriately?	Partly	Costs and health benefits were discounted at 5% in the base case and 3% in sensitivity analysis
1.7 Is QALY used as an outcome, and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	Partly	QALYs are used to represent health outcomes but it is unknown whether they were based on the EQ-5D
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	n/a	No other sectors are relevant
1.9 **Overall judgement:** Partially applicable There is no need to use section 2 of the checklist if the study is considered 'not applicable'.		
Other comments:		

Section 2: Study limitations (the level of methodological quality) This checklist should be used once it has been decided that the study is sufficiently applicable to the context of the guideline	**Yes/partly/no/unclear/ NA**	**Comments**
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Partly	Only 3 health states were used in the Markov model to represent patients with or without coronary heart disease. This may be an oversimplification of the events that could be avoided by diagnosing FH and providing lipid-modifying treatment.
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Partly	Although 10 years is may be a sufficient timeframe to capture all the important cost and health consequences, a lifetime time horizon would be consistent with the NICE reference case and allow the benefits to extension in life to be fully captured.
2.3 Are all important and relevant outcomes included?	Partly	Although the prevention of coronary heart disease is an important goal of case identification and lipid modification, other adverse events may also be prevented such as stroke.
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	The Dutch FH cohort is large and probably a good representation of the natural progression of the disease in a European population.
2.5 Are the estimates of relative intervention effects from the best available source?		Effectiveness of cascade screening was based on the author's own experiences in their centre. A review of the published literature would have been useful to at least

Ademi Z, Watts G F, Pang J, Sijbrands E J, van Bockxmeer , F M, O'Leary P, Geelhoed E, and Liew D. (2014). Cascade screening based on genetic testing is cost-effective: evidence for the implementation of models of care for familial hypercholesterolemia. Journal of Clinical Lipidology, 8, pp.390-400.		
		establish if these estimates are consistent with findings in other centres.
2.6 Are all important and relevant costs included?	Unclear	Scant details are provided on the resource use calculations adopted to calculate the cost of cascade screening.
2.7 Are the estimates of resource use from the best available source?	Unclear	Not provided
2.8 Are the unit costs of resources from the best available source?	Unclear	Not provided
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	No	An alternative strategy based on LDL-C thresholds rather than DNA testing was carried out as a sensitivity analysis rather than a discrete intervention. If this is a mutually exclusive valid option to DNA testing, this should have been included in incremental analysis with the cost effectiveness of the DNA cascade testing strategy compared against the LDL-C strategy rather than no cascade testing. This may have a material impact on the conclusions of the study. Insufficient detail was provided for this to be carried out by the update analyst.
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Partly	Probabilistic sensitivity analysis was carried out but inappropriate distributions were used to represent uncertainty around important parameters.
2.11 Is there any potential conflict of interest?	Yes	The authors have an interest in demonstrating the services they provide are cost effective.
2.12 **Overall assessment:** Potentially serious limitations		
Other comments: • Triangular distributions used for relative risk of fatal and nonfatal CHD events. Lognormal is preferred for this type of parameter. The choice to use a triangular distribution may have made the intervention more cost effective than it otherwise would have been to the extent that a lognormal distribution would have allowed less effective relative risks greater than the upper range of the triangular distribution, 0.3. • Uniform distribution used for costs. Gamma or lognormal distributions are preferred for this type of parameter. It is difficult to predict whether this would have favoured the intervention or comparator. • Age-dependent population norms for utilities not used		

Chen C X, and Hay J W. (2015). Cost-effectiveness analysis of alternative screening and treatment strategies for heterozygous familial hypercholesterolemia in the United States. International Journal of Cardiology, 181, pp.417-24.		
Section 1: Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5) This checklist should be used first to filter out irrelevant studies.	**Yes/partly/no/unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Partly	Common population mutations in the US may vary from those identified in the European population, but evidence from European populations has been used in the analysis Males only
1.2 Are the interventions appropriate for the review question?	Partly	Genetic cascade screening is compared with lipid cascade screening but no screening and index case identification were not included in the analysis. The lipid cascade screening with adherence programme intervention is not really relevant to the decision-making context of the update.
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	It is likely the costs of the US health care system do not represent those incurred by the NHS
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	No	US societal perspective adopted
1.5 Are all direct effects on individuals included, and are all other effects included where they are material?	Yes	
1.6 Are all future costs and outcomes discounted appropriately?	Partly	3% NICE reference case is 3.5%
1.7 Is QALY used as an outcome, and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	Yes	
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	n/a	
1.9 **Overall judgement:** Partially applicable There is no need to use section 2 of the checklist if the study is considered 'not applicable'.		
Other comments: Two parameters in the model substantially limit the generalisability of this study to decision-making in the NHS. • The first year screening cost of US$5,528 far exceeds what would be incurred by the NHS. A sensitivity analysis found that genetic cascade screening was cost effective compared with lipid cascade screening for a first year screening cost of $1,830 and it is likely that the cost in the UK is less than this. • The 10mg dose of atorvastatin is less than the high potency treatment recommended by UK guidelines.		

Chen C X, and Hay J W. (2015). Cost-effectiveness analysis of alternative screening and treatment strategies for heterozygous familial hypercholesterolemia in the United States. International Journal of Cardiology, 181, pp.417-24.

Section 2: Study limitations (the level of methodological quality) This checklist should be used once it has been decided that the study is sufficiently applicable to the context of the guideline	**Yes/partly/no/unclear/NA**	**Comments**
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Partly	The Markov model based on 3 health states may oversimplify the health states relevant to the risks that lipid-modification hopes to address
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	
2.3 Are all important and relevant outcomes included?	Partly	The Markov model based on 3 health states may oversimplify the health states relevant to the risks that lipid-modification hopes to address
2.4 Are the estimates of baseline outcomes from the best available source?	Partly	The Simon Broome register is a reasonable source for FH specific risk adjustments but it is unknown whether this is the best-available source
2.5 Are the estimates of relative intervention effects from the best available source?	Partly	The reductions in cholesterol due to statins appear to be the same as the general population as per the Framingham study
2.6 Are all important and relevant costs included?	Yes	However, the cost of genetic testing far exceeds what is incurred by the NHS
2.7 Are the estimates of resource use from the best available source?	Yes	
2.8 Are the unit costs of resources from the best available source?	Yes	
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Partly	Inappropriate distributions used. Normal distributions used for transition probabilities and utilities. Triangle distributions used for hazard ratio of death after CVD event and disutility from statin medication in the pre-CVD state.
2.11 Is there any potential conflict of interest?	No	
2.12 **Overall assessment:** Potentially serious limitations		
Other comments:		

National Collaborating Centre for Primary Care. (2008). Familial Hypercholesterolaemia, appendix E, health economic modelling. , NICE Clinical Guideline 71, pp.. **Nherera L, Marks D, Minhas R, Thorogood M, and Humphries S E. (2011). Probabilistic cost-effectiveness analysis of cascade screening for familial hypercholesterolaemia using alternative diagnostic and identification strategies. Heart, 97, pp.1175-1181.**		
Section 1: Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5) This checklist should be used first to filter out irrelevant studies.	**Yes/partly/no/unclear/ NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	
1.2 Are the interventions appropriate for the review question?	Yes	
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	UK
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	Yes	NHS
1.5 Are all direct effects on individuals included, and are all other effects included where they are material?	Yes	
1.6 Are all future costs and outcomes discounted appropriately?	Yes	
1.7 Is QALY used as an outcome, and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	Yes	
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	n/a	
1.9 **Overall judgement:** Directly applicable There is no need to use section 2 of the checklist if the study is considered 'not applicable'.		
Other comments:		

Section 2: Study limitations (the level of methodological quality) This checklist should be used once it has been decided that the study is sufficiently applicable to the context of the guideline	**Yes/partly/no/unclear/ NA**	**Comments**
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	
2.3 Are all important and relevant outcomes included?	Yes	
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	Simon Broome register
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	TA94
2.6 Are all important and relevant costs included?	Yes	

National Collaborating Centre for Primary Care. (2008). Familial Hypercholesterolaemia, appendix E, health economic modelling. , NICE Clinical Guideline 71, pp.. **Nherera L, Marks D, Minhas R, Thorogood M, and Humphries S E. (2011). Probabilistic cost-effectiveness analysis of cascade screening for familial hypercholesterolaemia using alternative diagnostic and identification strategies. Heart, 97, pp.1175-1181.**		
2.7 Are the estimates of resource use from the best available source?	Yes	
2.8 Are the unit costs of resources from the best available source?	Yes	
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Partly	PSA conducted for journal article but not full guideline
2.11 Is there any potential conflict of interest?	Unclear	As per declarations of interest in full guideline for guideline committee
2.12 **Overall assessment:** very serious limitations		
Other comments: • The diagnostic definitions change according to strategy. For example, a true positive can have elevated LDL-C levels or be a carrier of the family mutation. That is, a person with a family mutation would be a true positive in a DNA strategy but not in the cholesterol strategy if they do not have raised cholesterol. Therefore, the results are not necessarily comparable between strategies. • The cost and QALYs per person from treatment were used to estimate total cost and QALY gain for each strategy by multiplying the number of index cases recruited by the cost and QALY gain per patient. This fails to take into account the QALYs (and costs) that would have been accrued by these people had they not been identified, overinflating the QALY gain of these strategies (and potentially cost).		

Appendix O: Cost-utility analysis of strategies to identify and diagnose familial hypercholesterolaemia

O.1 Introduction

Familial hypercholesterolaemia (FH) is characterised by an inherited genetic mutation which causes a high cholesterol concentration from birth. People with FH have a higher risk of coronary heart disease, particularly at younger ages (Nordestgaard 2013). Once diagnosed, treatement with statins substantially reduces the risk of coronary heart disease (Versmissen et al. 2008; Neil et al. 2008).

It is estimated that between 115,770 (based on a prevalence of 1 in 500) (Nordestgaard et al. 2013) and 266,272 (based on a prevalence of 1 in 217) (Benn et al. 2016) people in England and Wales have FH but only 15% of are currently diagnosed (Pedersen et al. 2010). Cascade testing, where the relatives of people currently diagnosed with FH are genetically tested to see if they carry the family mutation, is currently recommended in NICE CG71 but it has been estimated that only half of all carriers are likely to be identified using this strategy (Pedersen et al. 2010). Since the original guideline (NICE CG71) was published new evidence has been produced on the effectiveness of identifying FH in primary care and secondary care databases. It is the goal of this update and economic analysis to establish the clinical and cost effectiveness of these strategies compared with cascade testing. Strategies that involve case identification in primary and secondary care are in addition to cascade testing. That is, for example, once a person is diagnosed with FH in primary care, it is expected that their relatives are invited for cascade testing following identification of the family mutation in the new index case. This is supported by the existing literature on cascade testing included in the present economic systematic review, including the economic analysis conducted for the original guideline (NICE CG71; NCCPC 2008; Nherera 2011).

The resource impact of cascade testing is influenced by the cost of contacting relatives, the cost of genetic testing, administrative and staffing costs involved in patient advice and support before and after testing, the number of relatives able to be approached (usually dependent on where they live), the probability an index case agrees to cascade testing, and the probability a relative takes up the offer of cascade testing. There are three types of cascade testing. Indirect cascade testing occurs when index cases take responsibility for contacting relatives and informing them of their risk of having FH. Direct cascade testing involves a healthcare professional, usually a specialist nurse, making direct contact with potentially affected relatives and informing them about FH and the potential benefits of genetic testing. Direct cascade testing requires more resources but is thought to be more effective at eliciting participation by relatives in genetic testing. The third type of cascade testing is a combination of direct and indirect methods. Combination direct and indirect cascade testing was found to be most effective in the clinical review and used to represent cascade testing in this economic analysis.

The resource impact of new case identification in primary care is influenced by the cost of informatics setup and training in GP surgeries, contacting patients for further assessment, the likelihood those people identified actually have FH, the take up of further clinical assessment, the diagnostic performance of clinical assessment tools (particularly regarding their specificity and false positives that result in unnecessary genetic testing), the cost of referral to a lipid clinic and genetic testing, and the benefits gained from cascade testing the relatives of new index cases.

The resource impact of identifying new index cases that have already experienced an early myocardial infarction in secondary care databases is influenced by similar factors as those identified through GP surgeries except that this is usually conducted in the secondary care setting.

The committee determined that de novo economic modelling was required for the update because:

- The cost effectiveness of new index case identification in primary care and secondary care has not been investigated in any of the studies identified in the economic review.
- The cost of treatment (with atorvastatin) has decreased since the original guideline.
- The cost of genetic testing has decreased since the original guideline.
- The ability to differentiate between monogenic FH and polygenic hypercholesterolaemia due to developments in genetic testing is now an important part of the cascade testing pathway and its relative cost effectiveness.

O.2 Model overview

O.2.1 Interventions

The following strategies were compared in the analysis:

1. No case identification and no cascade testing
2. Genetic cascade testing of the relatives of people with a current clinical diagnosis of FH and a functional mutation in the LDLR, APOB or PCSK9 gene
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
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
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
6. Secondary care case identification, clinical assessment using the DLCN criteria, and cascade testing of the relatives of new identified index cases; in addition to cascade testing from currently diagnosed index cases
7. Primary care case identification, secondary care case identification, clinical assessment using the SB criteria, and cascade testing of the relatives of newly identified index cases; in addition to cascade testing from currently diagnosed index cases
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

Two alternative cascade testing strategies are currently recommended by NICE. CG71 recommends the use of genetic testing and lipid-based cascade testing in the event that a family mutation is not identified. The Quality Standard for FH recommends the use of cascade testing of monogenic FH index cases only, reflecting the development of the evidence-base since the clinical guideline was published. The lipid-based cascade testing strategy currently recommended by CG71 was not included in the analysis because only relatives of index cases with a monogenic mutation have a 50% chance of having FH. Topic experts advised that, where it is implemented, current practice is thought to follow the Quality Standard (genetic cascade testing from index cases with a monogenic mutation, not lipid-based cascade testing).

Universal screening for FH in children was assessed by the UK National Screening Committee and not recommended (UK National Screening Committee 2016) and has not been included in this analysis. Reverse cascade testing, where parents and siblings of children in whom FH has been diagnosed are tested for FH, effectively relies on the existence of universal screening for FH in children and has been excluded from this analysis. The strategies compared in this analysis are not universal screening interventions.

Economic analyses for NICE usually identify a strategy to represent current practice to serve as a comparator against which other strategies are compared. Topic experts advised that implementation of cascade testing in England is poor but has been taken up in some local areas. It is difficult to estimate whether strategy 1 or 2 best represents current practice so both have been included in this analysis.

O.2.2 Population

There are six subpopulations that have the potential to come in to contact with these strategies for which short term costs and long term health and cost consequences need to be accounted for:

1. People with a current clinical diagnosis of FH
2. Relatives of people with a current clinical diagnosis of FH
3. People identified in a primary care database as requiring further investigation because they have a total cholesterol level higher than 7.5 mmol/L recorded (potential new index cases)
4. Relatives of people identified in a primary care database who have FH
5. People who have experienced an early myocardial infarction (potential new index cases in secondary care)
6. Relatives of people who have experienced an early myocardial infarction who have FH

O.2.3 Pathways

This section provides a detailed description of the strategies and how each subpopulation is affected by the strategy. Figures representing each strategy in decision tree format can be found in the following section.

O.2.3.1 Strategy 1: No cascade testing and no case identification

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 actually have 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 currently diagnosed: Relatives with FH remain untreated and have a higher risk of myocardial infarction, angina and coronary heart disease. Relatives without FH (healthy relatives) are not included in long term modelling because their numbers do not change between strategies.
3. Primary care population with raised cholesterol: 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. All other people remain untreated in this strategy.

4. Relatives of new index cases in primary care: All people with FH remain untreated. People without FH (healthy people) are not included in long term modelling.
5. Secondary care population with early myocardial infarction: All people with FH and polygenic hypercholesterolaemia are treated with high-intensity statins for secondary prevention. Therefore, this subpopulation has no impact on incremental differences in long term costs and QALYs. They will incur short term costs in strategies that aim to identify people with early MI and FH (not this strategy).
6. Relatives of new index cases in secondary care: All people with FH remain untreated. People without FH are not included in long term modelling.

O.2.3.2 Strategy 2: Cascade testing from monogenic FH index cases

1. Currently clinically diagnosed FH: Most of this subpopulation incur a cost to undergo a genetic test to determine their family mutation. A proportion will have a functional mutation in the LDLR, APOB, or PCSK9 gene. The remainder are found to have a polygenic cause of their hypercholesterolaemia. All receive treatment with statins, ezetimibe, or statins and ezetimibe regardless of the outcome of the genetic test in the base case.
2. Relatives of currently diagnosed: Relatives of index cases found to have monogenic FH are contacted and offered genetic counselling and testing. Some of the relatives will take up the offer. Some of the proportion (~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 (healthy people) are not included in long term modelling. 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 myocardial infarction, angina and mortality due to coronary heart disease. Relatives who do not take up genetic testing and do not have FH are not included in long term modelling.
3. Primary care population with raised cholesterol: As per strategy1.
4. Relatives of new index cases in primary care: As per strategy 1.
5. Secondary care population with early myocardial infarction: As per strategy 1.
6. Relatives of new index cases in secondary care: As per strategy 1.

O.2.3.3 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. Currently clinically diagnosed FH: As per strategy 2.
2. Relatives of currently diagnosed: As per strategy 2.
3. Primary care population with raised cholesterol: Resource is required to set up informatics in GP surgeries. Those identified by the database search have their medical records examined by a practice nurse and invited for clinical assessment. Those patients that take up the invitation and are identified as having possible or definite FH (in the base case) during a clinical assessment with a nurse specialist are referred to a lipid clinic for genetic testing. Those identified as possible or definite FH either have monogenic FH (true positives) or not (false positives). False positives undergo a genetic test, overturning their initial clinical diagnosis, and enter the treated hypercholesterolaemia module. That is, although they do not have FH, coming into contact with a healthcare professional means they moved fromm an untreated to treated state. True positives undergo a genetic test to confirm their diagnosis and enter the treated FH module. Out of the people that the Simon Broome criteria determines do not have possible or definite FH, some will have monogenic FH (false negatives) and the remainder will not (true negatives). False negatives enter the treated FH module. Although the clinical assessment found (incorrectly) they did not have FH, they still have high cholesterol and have come into contact with a healthcare professional. Following NICE CG181, these people would be prescribed a high-intensity statin in the base case. True negatives are not included in long

term modelling. There is a proportion of people with FH and polygenic hypercholesterolaemia that are already on statins and enter the treated modules even if they do not take up the offer of clinical assessment.

4. Relatives of new index cases in primary care: Relatives of these new index cases are offered cascade testing and follow the same path as that specified for population 2 above. Whether they are offered cascade testing at all depends on the likelihood of potential new index cases being correctly identified as having FH. That is, the explanation for subpopulation 3 directly above.
5. Secondary care population with early myocardial infarction: As per strategy 1.
6. Relatives of new index cases in secondary care: As per strategy 1.

O.2.3.4 Strategy 4: Primary 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 3 with the exception of using the DLCN criteria as the clinical assessment tool with referral to a lipid clinic if they have probable or definite FH (score >5) in the base case.

O.2.3.5 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. Currently clinically diagnosed FH: As per strategy 2.
2. Relatives of currently diagnosed: As per strategy 2.
3. Primary care population with raised cholesterol: As per strategy 1.
4. Relatives of new index cases in primary care: As per strategy 1.
5. Secondary care population with raised cholesterol: 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. Those identified as possible or definite FH will turn out to have monogenic FH (true positives) or not (false positives). Out of the people that the Simon Broome criteria determines do not have possible or definite FH, some will have monogenic FH (false negatives) and the remainder will not (true negatives). True positives undergo a genetic test to confirm their diagnosis and enter the treated FH model. False positives also undergo a genetic test, overturning their initial diagnosis but still entering a treated hypercholesterolaemia model due to their high cholesterol. All people receive treatment for secondary prevention. The long term outcomes for this subpopulation are actually the same and do not change between strategies because they are treated with statins regardless of diagnosis. What does change is the short term cost they incur in the process of being diagnosed with FH and then the long term health and cost outcomes their relatives benefit from (if diagnosed) who otherwise may have remained untreated.
6. Relatives of new index cases in secondary care: Relatives of these new index cases are offered cascade testing and follow the same path as that specified for relatives in strategy 2. Whether relatives are offered cascade testing at all depends on the potential new index cases above being correctly identified.

O.2.3.6 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

The pathway here is the same as strategy 5 apart from using the DLCN criteria as the clinical assessment tool to determine referral to the lipid clinic (probable or definite FH, score >5).

O.2.3.7 Strategy 7: Primary care case identification, secondary care case identification, clinical assessment using the SB criteria, and cascade testing of the relatives of newly identified index cases; in addition to cascade testing from currently diagnosed index cases

The pathways of strategy 7 and 8 follows what has already been specified in previous strategies but now in combination.

1. Currently clinically diagnosed FH: As per strategy 2.
2. Relatives of currently diagnosed: As per strategy 2.
3. Primary care population with raised cholesterol: As per strategy 3.
4. Relatives of new index cases in primary care: As per strategy 3.
5. Secondary care population with early myocardial infarction: As per strategy 5.
6. Relatives of new index cases in secondary care: As per strategy 5.

O.2.3.8 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 with the DLCN criteria for clinical assessment (probable or definite FH, score >5 in the base case).

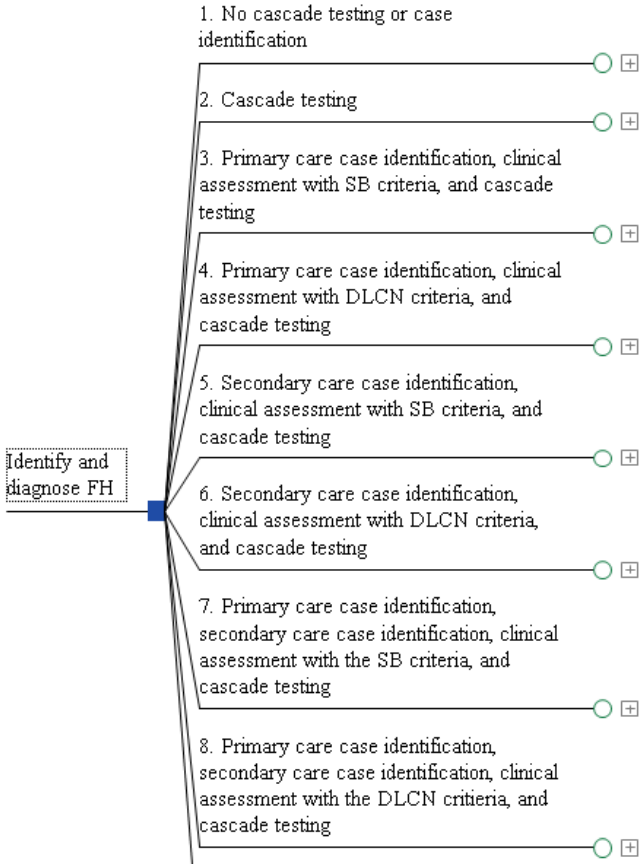
O.2.4 Structure

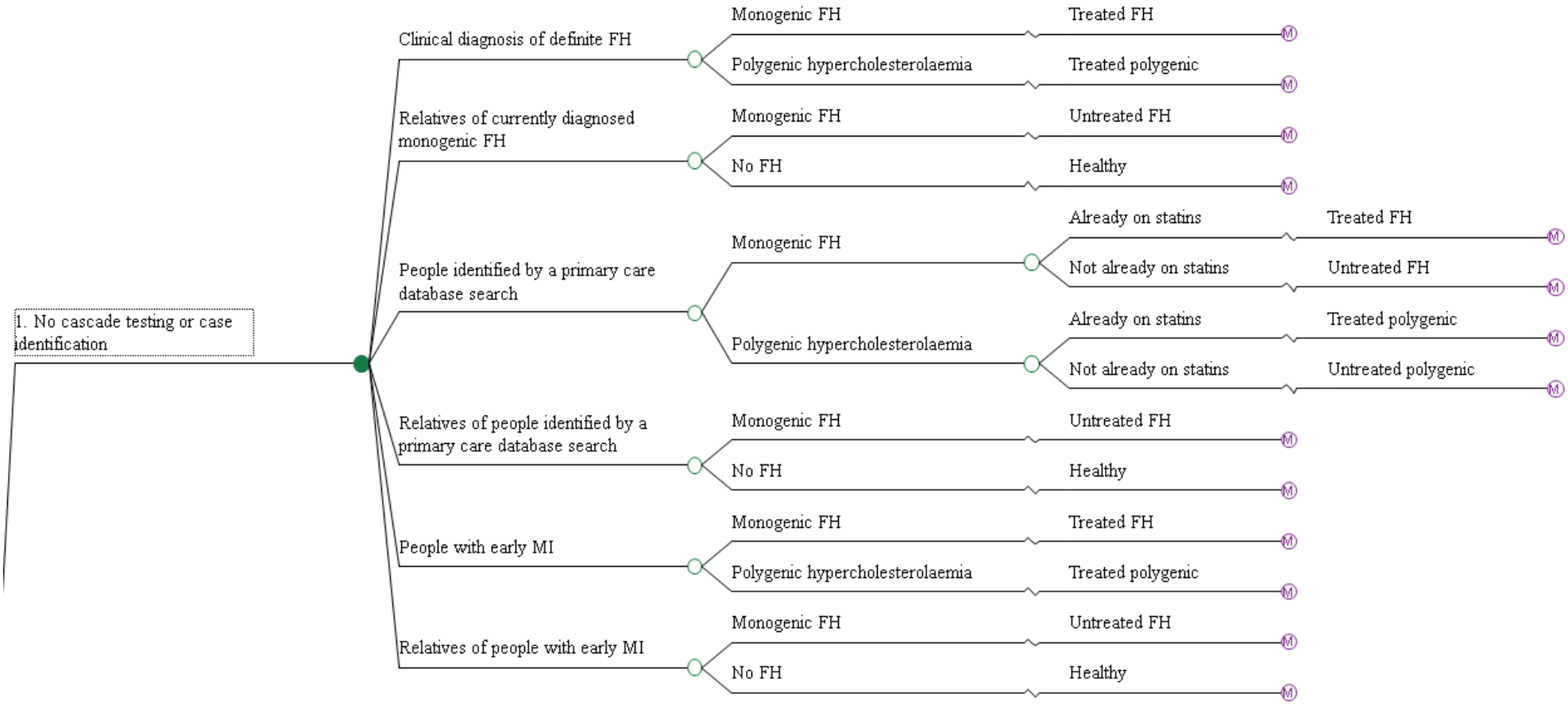
The structure of the economic model consists of five modules:

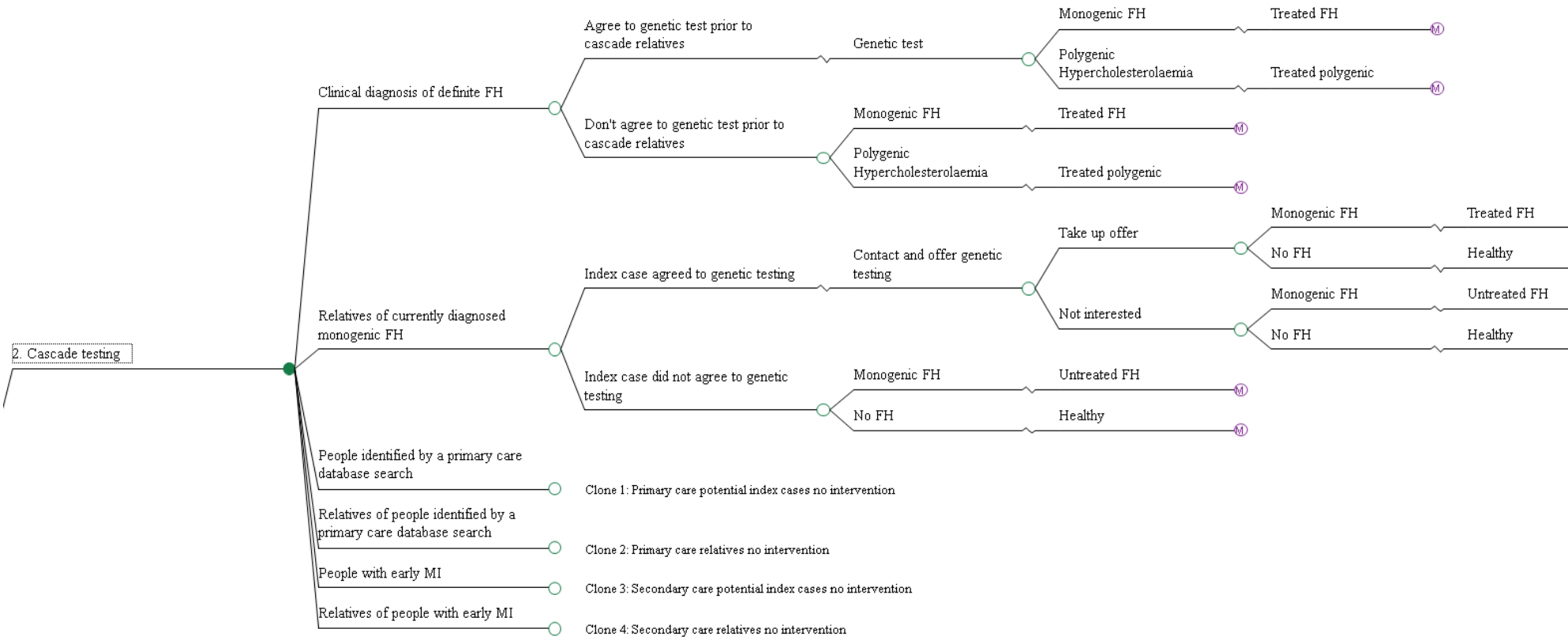
1. The decision tree module captures short term identification, diagnosis and cost outcomes. There is one subtree for each strategy and a pathway for each subgroup within each subtree.
2. The 'Untreated FH' module contains the summary payoffs from a Markov model to capture the long term consequences of untreated FH. People can enter this module if they are diagnosed as not having FH even though they actually do (false negative) or because they have not been identified and tested for FH simply because there is no opportunity to within that strategy. These payoffs were extracted from the cost-effectiveness analysis of low-intensity, medium-intensity and high-intensity statin treatment for the primary and secondary prevention of cardiovascular disease in NICE CG181 (lipid modification). This model has 8 alive health states (plus 7 transition states) and has been adjusted to account for the different risk profile of people with FH. Further detail can be found in the economic modelling report for CG181 and information how it was adjusted to account for the FH population can be found in the next section on input parameters.
3. The 'Treated FH' module contains the summary payoffs from a Markov model that captures the long term consequences of treated FH. This is based on adjusted CG181 module explained in module 2 above with treatment effects based on atorvastatin 80 mg and additional information is provided in the next section on input parameters.
4. The 'Untreated polygenic hypercholesterolaemia' module contains the summary payoffs from the unadjusted CG181 Markov model. Reference costs have been updated to the most recent financial year for which reference costs are available (2014-15).
5. As per module 4 with treatment effect based on atorvastatin 20 mg and updated costs. Atorvastatin 20 mg is recommended in NICE CG181.

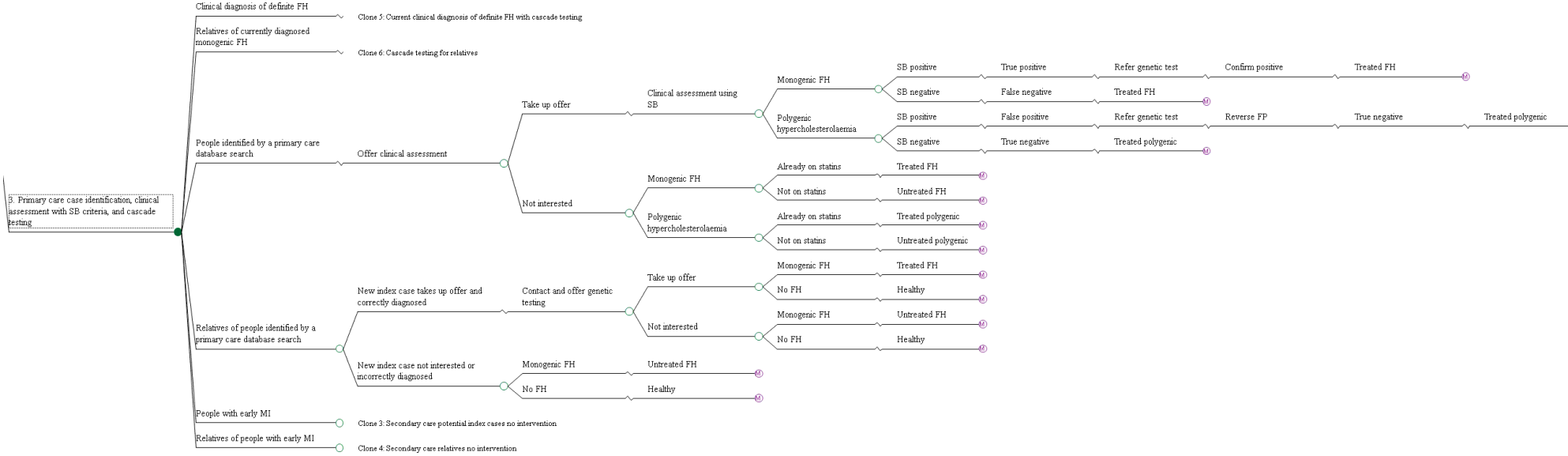
The following diagrams present the structure of the short term identification and diagnosis module.

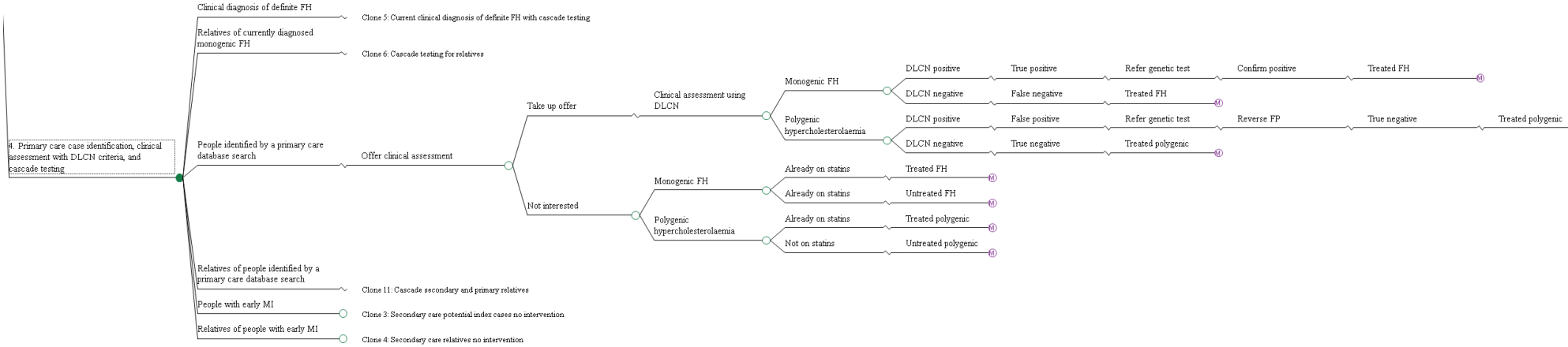
Figure 12: Structure of case identification and diagnosis module

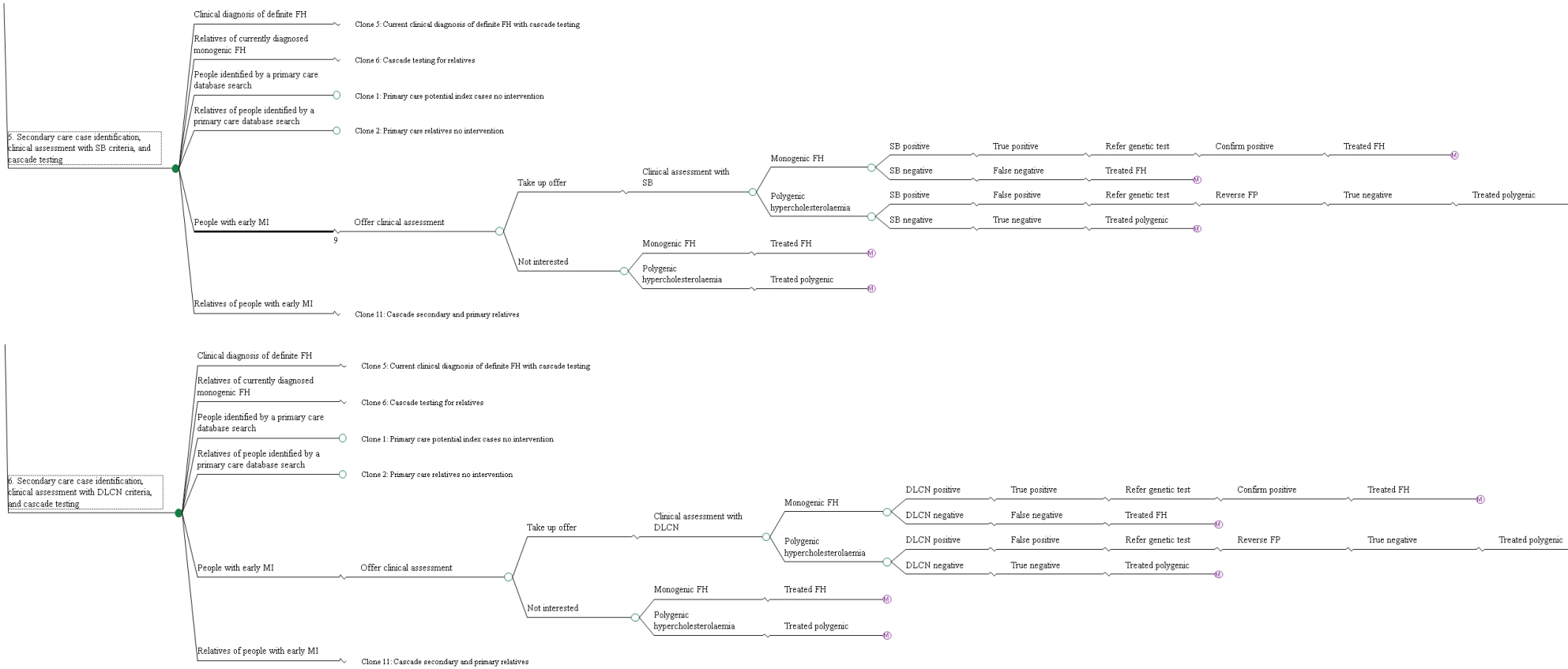


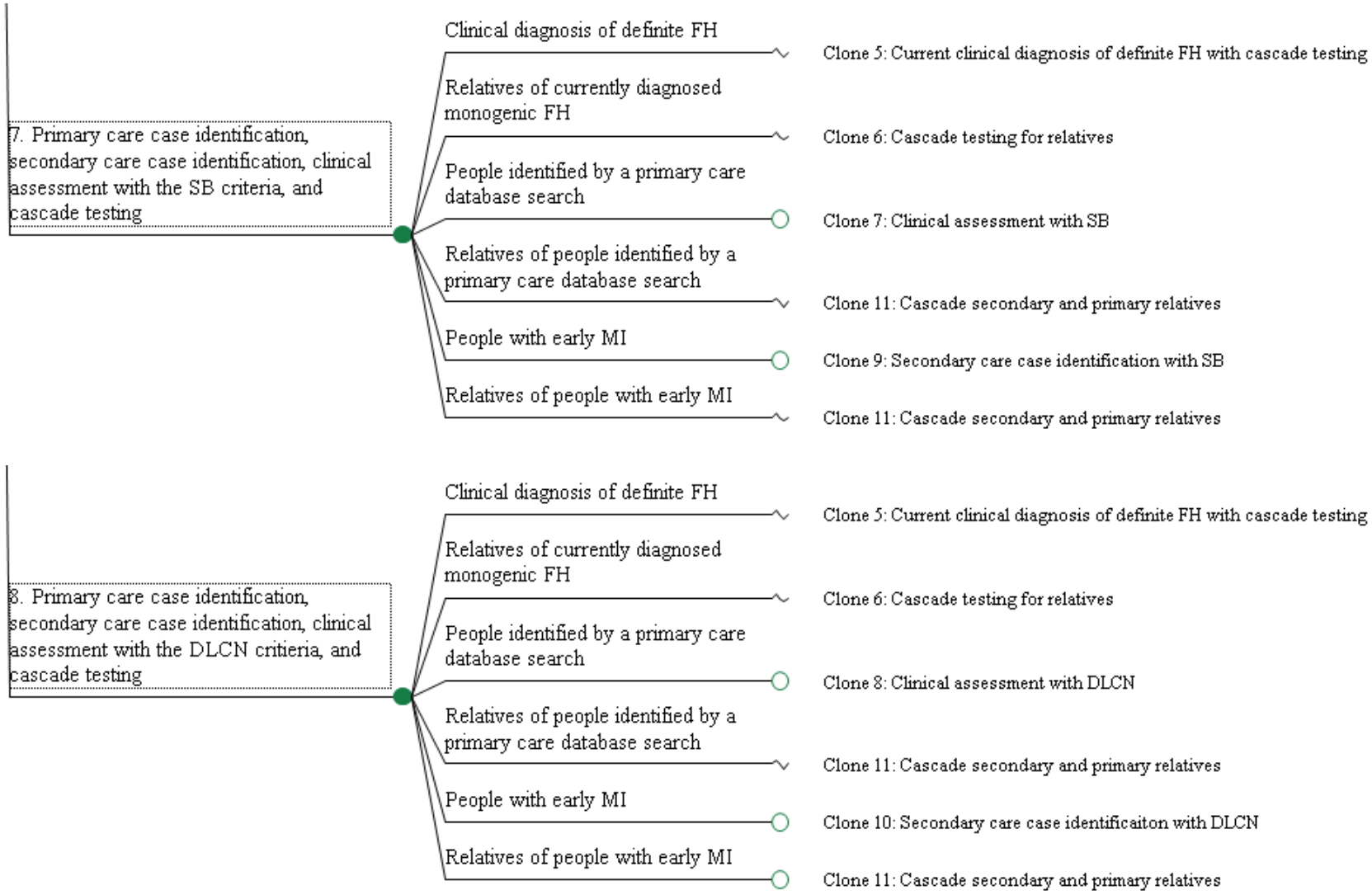

1. No cascade testing or case identification
Clinical diagnosis of definite FH
Monogenic FH
Treated FH
Polygenic hypercholesterolaemia
Treated polygenic
Relatives of currently diagnosed monogenic FH
Monogenic FH
Untreated FH
No FH
Healthy
People identified by a primary care database search
Monogenic 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

O.2.5 Time horizon, perspective and discount rate

The analysis follows the NICE reference case by adopting a lifetime time horizon, the NHS & personal social services (PSS) perspective for costs and a discount rate of 3.5%. Some results are provided for the short term identification and diagnosis module only to aid decision-making.

O.2.6 Outcomes

The model calculates the following outcomes:

- Expected cost per person per strategy
- Total cost per strategy
- Cost per newly treated FH
- Cost per newly treated polygenic hypercholesterolaemia
- Incremental cost-effectiveness ratio (ICER) in terms of cost per quality adjusted life year (QALY)
- Net monetary benefit (NMB)

The ICER is calculated by dividing the difference in costs associated with two alternatives by the difference in QALYs. The optimal strategy is the one with the highest ICER below NICE's cost-effectiveness threshold of £20,000 to £30,000 per QALY after dominated and extendedly dominated options have been excluded because this is the strategy that maximises health benefits for an acceptable opportunity cost. A strategy is dominated and ruled out if another intervention is less costly and more effective. A strategy is extendedly dominated and ruled out if a combination of two other options is less costly and more effective.

Net monetary benefit is calculated by multiplying the health benefit in terms of QALYs by the cost-effectiveness threshold and subtracting the cost of the strategy. The decision rule here is that the strategy with the greatest NMB should be recommended. A £20,000 per QALY threshold has been adopted to calculate NMB in this analysis.

Both methods of calculating cost-effectiveness yield exactly the same optimal strategy. NMB is used as the main outcome measure due to the relative ease of computation and comparing results in sensitivity analysis.

O.2.7 Assumptions

The following assumptions were made in consultation with the committee:

- Genetic testing has perfect sensitivity and specificity. The committee discussed the potential impact of variants of unknown clinical significance (VUS) and determined not to include this because VUS occur in only around 5% of genetic tests (and not at all in testing relatives of mutation positive cases) and 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 corrected by subsequent genetic testing and converted to a true positive (this assumption was not the subject of sensitivity analysis but its effect is explored in the discussion section). A false negative clinical diagnosis is possible and this is not corrected by a subsequent genetic test because this cohort would not be referred for additional testing.
- 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 cost) of strategies that involve case identification in secondary care stems from cascade testing and correctly diagnosis the relatives of new index cases.

- A proportion of people with previously undiagnosed monogenic FH identified by a primary care database search who do not come into contact with a healthcare 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 (Robson et al. 2016).
- If people with monogenic 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 additional contact with primary care. That is, false negatives are counted as treated FH in the long term module even though they do not have a genetic test.
- 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. The probability of take up adopted for each subgroup was taken from published literature included in the clinical review and agreed with the committee.
- There is 100% adherence to the treatment once disease is diagnosed. This is consistent with the lipid modification model. The focus of the model is case identification and diagnosis and the committee 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 assessed as minor as efficacy estimates for statins were drawn from trials that contained a proportion of non-adherents.
- 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 conservativey small number of relatives assumed to be identified per index case.
- Crossover has not been implemented 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.

O.3 Input parameters

O.3.1 Identification and diagnosis module

The key input parameters and their sources are provided in Table 37. These parameters were informed as much as possible by the clinical review.

O.3.1.1 Clinical parameters

People with a current clinical diagnosis of FH

The number of people with a current clinical diagnosis of FH, 18,000, was informed by an audit of lipid clinics in the United Kingdom in 2010 (Pedersen 2010). This is based on the actual number of FH patients reported to be under active management by the audited lipid clinics, and represents ~15% of the lower estimate of FH prevalence in the general population, 120,000.

Out of the people with a current clinical diagnosis of FH, only a proportion will actually have monogenic FH. Kerr et al. (2017) provided an estimate based on the experiences of the Welsh, Scottish and Wessex FH services, 22.98%.

The prevalence of FH in the general population is widely noted in the literature as 1/500 (for example, Nordestgaard 2013) and is thought to represent a low estimate of actual prevalence. A conservative approach was taken and this figure was used in the base case. Recent studies have reported prevalence in the general population up to 1 in 217 and this was used in sensitivity analysis (Benn 2016). A prevalence of FH-mutation carriers of 1/273 in UK children has recently been reported (Wald et al NEJM 2016). This value was not used directly in the model but was used qualitatively to validate the prevalence of FH predicted by the different possible search criteria.

People identified by a primary care database search

The adult population of England and Wales was sourced from the Office of National Statistics (2015). This was used to represent the number of people registered in primary care databses.

The proportion of people in primary care databases identified for further investigation by a search, and the prevalence of FH within this group, was informed by a single study. A single study was preferred because of the relationship that exists between the threshold of total cholesterol or LDL-C and the likelihood of having FH. Four main criteria were used when selecting the most appropriate study:

1. population was representative of people registered with GP practices in England and Wales;
2. diagnosis of FH was based on genetic testing;
3. the study reported both the number or proportion of people with raised cholesterol and the proportion of those people that had FH; and
4. resulted in general population prevalence of FH within expected limits when combined with other parameters of the model.

Eleven studies were considered to inform these two parameters. Seven studies were those included in the clinical review (Bell 2014b, Gray 2008, Green 2016, Kirke 2015, Norsworthy 2014, Qureshi 2016, Troeung 2016) and another four were identified by the topic experts as potentially useful for economic modelling (Weng 2015, Benn 2016, Khera 2016, Futema 2015). Five studies were not appropriate for the model because diagnosis was based on clinical assessment rather than genetic testing (Weng 2015, Gray 2008, Qureshi 2016, Troeung 2016, Green 2016). Another two studies conducted genetic testing but only for people with positive clinical assessment findings so the prevalence of FH would not have taken account of false negative clinical assessment results (Kirke 2015, Bell 2014b). Four studies reported the results of genetic testing for the whole sample with raised cholesterol (Futema 2015, Norsworthy 2014, Benn 2016, Khera 2016). Norsworthy et al. (2014) provided insufficient detail on how the sample taken forward for testing was selected from the Generation Scotland: Sottish Family Health Study sample of 24,000 people to allow meaningful calculation of these parameters for the model. Khera et al. (2016) reported the proportion of FH mutations for several bands of LDL-C in an American population but the implied general population prevalence of FH was too high (1/120 to 1/80) to be representative of the UK general population. Benn et al. (2016) reported the prevalence of FH for various bands of LDL-C in a large Danish population but the implied general population prevalence was too low for some stratifications (for example, 1/930 to 1/3190). Futema et al. (2015) genetically tested samples from the Whitehall II cohort of UK public service employees, broadly (although somewhat older and based in one geographical area) representative of people registered in primary care databases that reported total cholesterol greater than 9.3 mmol/L. The implied general population prevalence based on this data and the relatives that would be found through cascade testing was 1/340, falling between the

commonly adopted estimates used in the literature of 1/200 to 1/500. Therefore, the study by Futema et al. (2015) was used to inform the proportion of people in a primary care database that require further investigation and the prevalence of FH in this group.

Within any primary care database, only a certain portion of patients will actually have their cholesterol recorded. This was estimated to be 31% based on the finding by Futema et al. (2015) that 7.3% of adults with a cholesterol reading in the Whitehall II cohort had total cholesterol >7.5 mmol/L, combined with the finding by Qureshi et al. that 831 people out of ~36,000 in a real-world primary care database required further investigation based on their total cholesterol level >7.5 mmol/L (831/(7.3% x ~36000) = approx. 31%). This estimate was acknowledged to be uncertain and was the subject of sensitivity analysis (although varying this parameter only materially affects the overall resource impact rather than the cost effectivenss of the different strategies 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 work place identification cohorts of an Australian study included in the clinical review (Kirke 2015), 26%, varied up to 50% in sensitivity analysis.

A proportion of people in primary care databases will already be on statins regardless of intervention or take up. This proportion was informed by an evaluation of the NHS Health Check which found that 19.3% of people were prescribed lipid modification following the health check. This was varied down to 10% and up to 99% in sensitivity analysis.

People with early MI

The prevalence of FH in people with early MI is expected to be greater than the general population due to the higher risk of coronary heart disease. Wald et al. (2015) estimated this to be 1.3%. De Backer et al. (2015) provided an estimate of 8.3% but this was based on definite and probable scores from the DLCN criteria. Because this was not based on genetic diagnosis, it could not be used as the base case but was used to inform the upper limit for sensitivity analysis.

The take up of clinical assessment and genetic testing by people with early MI was also informed by Wald et al. (2015), with 72.5% agreeing to be tested for FH.

Relatives

The number of relatives approached for cascade testing per index case was estimated to be 2.22 based on the experience of the Welsh, Scottish and Wessex FH services as reported by Kerr et al. (2017). Although based on actual service experience, topic experts were concerned this was too low and this was increased to 12 first, second and third degree relatives per index case in sensitivity analysis based on the assumptions adopted in the 2009 NICE CG71 costing report.

The take up of clinical assessment by relatives was informed by a study included in the clinical review (Hadfield 2009). Although this study reported take up for relatives of people with a current clinical diagnosis, no data was identified for relatives of people with early MI or new index cases identified by a primary care database search so the same take up was used for all three groups of relatives. This was varied for each relative subpopulation independently in sensitivity analysis.

Table 37: Input parameters for current index cases, potential new index cases and relatives

Parameter	Amount	Source
People with a current clinical diagnosis of FH (current index cases)		

Parameter	Amount	Source
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)
Proportion of current clinical diagnosis with definite FH with monogenic mutation	22.98%	Welsh, Scottish & Wessex FH services, cited in Kerr et al. 2017
Prevalence monogenic FH in general population	0.20%	Nordestgaard 2013, 1 in 500, conservative lower limit found in literature
Take up of genetic testing by people with a current clinical diagnosis of FH prior to cascade testing	84.10%	Median from clinical review
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)
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)
Proportion of people with high cholesterol already on statins	19.30%	Robson 2016, NHS Health Check
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
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
Take up of clinical assessment and genetic testing by people with early MI	72.50%	Wald et al. 2015 (% excluding declined and too unwell)
Prevalence of MI in general population	0.23%	Prevalence MI age<55 from Bhatnagar 2015, adjusted for age and sex from ONS 2015
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

Parameter	Amount	Source
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.
Probability tested relative has monogenic FH	50.89%	Welsh, Scottish & Wessex FH services, cited in Kerr et al. 2017
Take up by relatives of cascade testing from currently diagnosed FH population	59.89%	Clinical review: Hadfield 2009
Take up by relatives of clinical assessment and genetic testing from people identified in primary care	59.89%	Clinical review: Hadfield 2009
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

The results of the meta-analyses from the clinical review were used to inform the sensitivity and specificity of clinical assessment tools. In the base case analysis a 'rule out' profile was used for referral to a lipid clinic and genetic testing (Simon Broome possible and definite; DLCN probable and definite (score >5). By adopting a lower threshold, the clinical assessment tool was used to 'rule out' disease (high sensitivity) in the base case at the expense of referring many false positives (low specificity). This may be undesirable if the cost of correctly diagnosing the false positives outweighed the benefit of correctly diagnosing people that do have FH through minimising false negatives.

In a sensitivity analysis, clinical assessment tools were used as 'rule in' test where only people with definite FH were referred for genetic testing. Increasing the threshold increases the level of confidence (due to higher specificity) that a person has FH before being referred to a lipid clinic at the expense of missing some people that do have FH (false negatives, lower sensitivity). This approach also reduces short term costs because less people are referred for genetic testing. This may be undesirable if the benefits gained by identifying and treating disease are likely to outweigh the cost of correcting false positive diagnoses. In other topics the health and cost consequences of inappropriate treatment provided to false positives also needs to be taken into account but in the present model there are no false positives by the end of the diagnostic module due to genetic testing that occurs following clinical assessment and the assumption that genetic testing has perfect diagnostic accuracy.

Table 38: Sensitivity and specificity of clinical assessment tools

Clinical assessment tool and threshold	Sensitivity or specificity
Sensitivity Simon Broome possible or definite FH	0.890
Specificity Simon Broome possible or definite FH	0.287
Sensitivity Simon Broome definite FH	0.360
Specificity Simon Broome definite FH	0.940
Sensitivity DLCN probable, definite FH (>=6)	0.861
Specificity DLCN probable, definite FH (>=6)	0.457
Sensitivity DLCN definite FH (>8)	0.567
Specificity DLCN definite FH (>8)	0.802

O.3.1.2 Short term costs

The cost of each strategy is provided in Table 43. Note 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. 2017 and are based on the resource use in the Welsh, Scottish and Wessex FH services with the latest costs from the PSSRU 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 39: 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 40: 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 41: 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		

Action	Resource	Amount
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 42: Summary of unit costs

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 2016 (resource use Welsh FH service, unit costs PSSRU)
Healthcare and admin staff inputs index case testing mutation negative cases (per person)	£199.74	Kerr 2016 (resource use Welsh FH service, unit costs PSSRU)
Healthcare and admin staff inputs relative testing mutation positive cases (per person)	£279.07	Kerr 2016 (resource use Welsh FH service, unit costs PSSRU)
Healthcare and admin staff inputs relative testing mutation negative cases (per person)	£174.67	Kerr 2016 (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

Model Input	Cost	Source
Lipid clinic/hospital administration assistant	£24.00	Curtis 2015(PSSRU), Allied health professional support worker
Lipid profile	£3.05	CG181 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 43: 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	

Total cost of each strategy, adjusted for the probability of individual resource use		
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

Total cost of each strategy, adjusted for the probability of individual resource use		
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)

Total cost of each strategy, adjusted for the probability of individual resource use		
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	

Total cost of each strategy, adjusted for the probability of individual resource use		
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	

Total cost of each strategy, adjusted for the probability of individual resource use		
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	

Total cost of each strategy, adjusted for the probability of individual resource use		
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
	£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	

O.3.2 Long term costs and QALYs for treated and untreated polygenic hypercholesterolaemia

O.3.2.1 Long term clinical inputs

On the advice of the committee, the lipid modification model (NICE CG181) 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 quality-adjusted life years. The CG181 model allows the user to specify underlying risk scores 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 HRQoL and mortality. The probabilities of these events happening are reduced by the use of statins. No changes were made to the clinical aspects of this model for the polygenic cohorts. Treatment was based on atorvastatin 20mg. A full description of the model can be found in the appendices of CG181.

O.3.2.2 Long term costs

The cost of cardiac events was updated to account for the latest NHS reference costs (2015-16). 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.

Table 44: 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

PROCEDURES	Unit cost	Source of cost	Detail of source
(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

O.3.3 Long term costs and QALYs for treated and untreated familial hypercholesterolaemia

The lipid modification model contained four health states that are at an increased risk of occurring in people with FH:

- Stable angina
- Unstable angina
- Myocardial infarction
- Death due to cardiovascular disease, of which coronary heart disease mortality is a component

The risk of first events was adjusted in the model as well as the risk of these events occurring subsequent to other health states.

The risk of the following events was left the same as the general population:

- Transient ischaemic attack
- Stroke
- Heart failure
- Peripheral artery disease

Three sources were considered to inform the higher risk of cardiac events due to FH. Benn et al. (2016) 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. However, this study was based on a Danish cohort and odds ratios are not reported separately by age and sex. Khera et al. (2016) provide a summary odds ratio for CAD of 3.8 (95% CI 2.6 to 5.4). However, this study was based on an American cohort and odds ratios are not reported by age or sex. The Simon Broome Register Group (1999 and personal communication Humphries January 2017) provided data on the mortality of a UK cohort over multiple decades with standardised mortality ratios reported by age and sex. This data also provided results with males and females combined which was useful for the risk of subsequent events in the lipid modification model which used the same probabilities for males and females (subsequent events only). Therefore, the Simon Broome Register data was used to inform this parameter. One limitation of this data was it recorded mortality only. Therefore, the increased risk of mortality due to FH was extrapolated to represent non-fatal events as well. Extrapolating mortality data to represent non-fatal cardiac events was

consistent with prior economic analyses on FH (Kerr et al 2017; Chen 2015, Nherera 2011, NCCPC 2008). These baseline relative risks are provided inTables 45-47.The Simon Broome Register data was split into pre-1991 and post-1991 deaths, and all deaths combined, with the pre-1991 data representing untreated FH in an era before statins. There was less data for pre-1991 than post-1991. For example, there were only 2 deaths in males of 60-79 years of age. This lack of statistical power lead to a counter-intuitive finding of a relative risk 0.76. That is, FH had a protective effect for men in that age group. Although it may be plausible due to a survivor effect, it may have lead to anomalies in the model. The combined data provided more statistical power with relative risks in the right direction and this was used to inform the model. It was recognised this was a conservative approach with a large portion of this data subject to reduced risks due to statin treatment. But there was still a four-times greater and five-times greater risk for males and females respectively of coronary heart disease in the 40-59 age group based on this combined data. In males the relative risk of ~4 was similar in pre and post 1991 data. In females the RR halved from ~10 to 5 after 1991 but the pre-1991 data was based on very few patients. The fact that most of the data came from patients with treated FH vs the general population was a limitation as what the long term model required was a relative risk of CVD in FH vs non-FH in people with a very high total cholesterol. If it can be inferred that people with treated high cholesterol have a similar risk to the general population then these data would be a reasonable proxy, however. It was recognised that although uncertain, these were the best data available but the RRs should be the subject of extreme sensitivity analysis (halving and doubling relative to 1).

Table 45: Relative risk of coronary heart disease due to FH in males (first events)

Age	Relative risk
40	4.0028
45	4.0028
55	4.0028
65	1.6199
75	1.6199
85	1.6199

Table 46: Relative risk of coronary heart disease due to FH in females (first events)

Age	Relative risk
40	5.133
45	5.133
55	5.133
65	2.2827
75	2.2827
85	2.2827

Table 47: Relative risk of coronary heart disease due to FH in males and females (subsequent events)

Age	Relative risk
40	4.179
45	4.179
55	4.179
65	1.8842
75	1.8842
85	1.8842

The treatment effect in terms of relative risk of CVD events due to appropriate treatment with lipid modification is provided inTable 48. There has been no change to the figures used in CG181 for either the polygenic or familial hypercholesterolaemia populations due to a lack of evidence on the adult FH population identified in the clinical review. Placebo-controlled trials have not included people with FH because it is unethical to withhold treatment from patients with severe hypercholesterolaemia and 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 The committee suggested that relatively greater improvements might be seen in people with FH, however, so a sensitivity analysis was conducted where the treatment effect was assumed to bring CVD risk in people in FH down to the values in treated people with polygenic hypercholesterolaemia.

Table 48: Treatment effect on CVD risk

CVD event	Relative risk
Stable angina	0.46
Unstable angina	0.46
Myocardial infarction	0.46
Transient ischaemic attack	0.8
Stroke	0.8
Heart failure	1
Peripheral artery disease	0.46
Cardiovascular mortality	0.73
Non-cardiac mortality	0.96

Note that although the relative treatment effect was the same as that used in the lipid modification model, the absolute risk of CHD for treated FH was still raised compared with the general and polygenic populations. Under treatment, the 10-year CVD risk for people with FH was typically similar to the untreated polygenic cohort of the same age and sex. Male sub populations are included in Table 48a below (the risks are broadly similar for females). Total CVD risks are higher than QRISK because they include the probability of developing Heart Failure and PAD:-

Table 48a: Example 10 year CVD risks for sub populations within the model and alternatives explored in sensitivity analysis

Age (Males)	Equivilent polygenic QRISK	Base Case		Low RR with FH		High RR with FH		High RR + High Treatment Effect	
		Untreated	Treated	Untreated	Treated	Untreated	Treated	Untreated	Treated
40	30%	78%	51%	62%	38%	94%	72%	94%	63%
40	25%	70%	44%	54%	32%	89%	63%	89%	55%
40	20%	60%	36%	45%	26%	81%	54%	81%	46%
40	15%	49%	28%	35%	20%	69%	43%	69%	36%
40	10%	35%	19%	25%	13%	53%	30%	53%	25%
50	30%	77%	51%	61%	38%	93%	72%	93%	64%
50	25%	69%	44%	53%	32%	88%	64%	88%	56%
50	20%	59%	36%	44%	26%	80%	54%	80%	47%

Age (Males)	Equivilent polygenic QRISK	Base Case		Low RR with FH		High RR with FH		High RR + High Treatment Effect	
		Untreated	Treated	Untreated	Treated	Untreated	Treated	Untreated	Treated
50	15%	48%	28%	34%	20%	68%	43%	68%	37%
50	10%	34%	19%	24%	13%	52%	30%	52%	25%
60	30%	47%	31%	43%	29%	55%	36%	55%	31%
60	25%	40%	26%	37%	24%	48%	30%	48%	26%
60	20%	33%	21%	30%	19%	39%	24%	39%	21%
60	15%	25%	16%	23%	14%	30%	18%	30%	16%
60	10%	17%	10%	15%	10%	21%	12%	21%	10%
70	30%	46%	32%	42%	30%	54%	36%	54%	32%
70	25%	39%	26%	36%	25%	47%	30%	47%	26%
70	20%	32%	21%	29%	20%	39%	24%	39%	21%
70	15%	24%	16%	22%	15%	30%	18%	30%	16%
70	10%	17%	11%	15%	10%	20%	12%	20%	11%

The ‘high’ and ‘low’ risks here were calculated by arbitrarily doubling and halving the RR of FH relative to 1. The increased treatment effect was calculated using the lower confidence interval of the RRs associated with statin use for primary and secondary prevention. These are extreme values and not underpinned by an evidence base in the population with confirmed FH. The RRs are in Table 48b:-

Table 48b: Relative CVD risks for Males and Females with FH

Male	Base Case	SA Low RR	SA High RR
40	4.0028	2.5014	7.0056
45	4.0028	2.5014	7.0056
55	4.0028	2.5014	7.0056
65	1.6199	1.30995	2.2398
75	1.6199	1.30995	2.2398
85	1.6199	1.30995	2.2398
Female			
40	5.133	3.0665	9.266
45	5.133	3.0665	9.266
55	5.133	3.0665	9.266
65	2.2827	1.64135	3.5654
75	2.2827	1.64135	3.5654
85	2.2827	1.64135	3.5654
Both			
40	4.179	2.5895	7.358
45	4.179	2.5895	7.358
55	4.179	2.5895	7.358
65	1.8842	1.4421	2.7684
75	1.8842	1.4421	2.7684

Male	Base Case	SA Low RR	SA High RR
85	1.8842	1.4421	2.7684

Two studies supported this continued increased absolute risk associated with FH despite treatment (Simon Broome Register Group 1999; Mohrschladt et al. 2004) but another two found this risk was reduced to the same level as the general population (Versmissen et al. 2008; Neil et al. 2008). 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 would have been based on a clinical diagnosis (rather than genetic) and, therefore, contained a large polygenic cohort, a conservative approach was taken and higher absolute risk of CHD (same relative risk due to treatment as the general population) retained with treatment. The treatment effects were heightened to the top of their observed confidences interval in all clinical domains in sensitivity analysis to move treated risk closer to that of the overall population.

One limitation of this method is that it calculates costs and QALYs incorrectly for the very small subpopulation of this model who have already had an early MI. This limitation is minor, however, as this population is exactly the same among strategies so any error will cancel out and relative cost effectiveness results will be unaffected.

O.3.3.1 Long term costs

For the FH cohort, the cost of treatment was based on the proportion of people on high potency medicines from the Welsh, Scottish and Wessex FH services (Kerr et al., 2017) (Table 49). The proportion prescribed does not sum to 100% because some people take statins alone, some take ezetimibe alone, and some are prescribed both.

Table 49: 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	

O.3.4 Expected long term costs and QALYs, FH and polygenic

After adjusting for age, the Markov modules result in the following expected payoffs for the four cohorts (Table 49a). These figures represent the expected total, discounted cost and health outcomes experienced by each cohort over their lifetimes. That is, it is a summary of each of the four long term modules. Differences in QALYs and costs between males and females are predominantly due to different baseline risks of cardiovascular events and different adjustments in those risks due to FH. As might be expected, 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% having 10% to 100% having 30% in sensitivity analysis.

Table 49a – Expected lifetime costs and QALYs under base case assumptions

Payoff	Treated FH	Untreated FH	Treated polygenic	Untreated polygenic
Male - cost	£12,045.05	£12,347.77	£6,270.82	£6,286.97

Payoff	Treated FH	Untreated FH	Treated polygenic	Untreated polygenic
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

Table 49a shows 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 at younger ages due to the large reduction in CVD event costs outweighing the cost of high intensity statins.

O.3.5 Sensitivity analysis

One-way sensitivity analysis was conducted on several parameters (Table 50).

The number of relatives approached for cascade testing in the base case was 2.22 based on the FH services in Wales, Scotland and Wessex as reported by Kerr et al. (2017). The committee viewed this figure as overly conservative as it was based on an incomplete national cascade testing service in England. Families are geographically spread and if most of the relatives for any given index case are in an area that does not have a FH service for screening relatives then the yield from the index cases is minimal. In the committee's view, it should be possible to achieve a higher yield from cascade testing which is likely once the service is provided across England. Therefore, this parameter was testing in sensitivity analysis up to 12 relatives per patient based on the assumption used in a previous NICE costing report.

The other parameters tested and their sources are listed below.

Table 50: Parameters varied in 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

Parameter	Low value	High value	Source
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

In addition, a 'rule in' profile was used in a sensitivity analysis for the clinical assessment tools where a higher threshold for referral to lipid clinics was adopted. In the base case, both possible and and definite findings using the Simon Broome criteria and DLCN criteria scores greater than 5 were referred for genetic testing. In this sensitivity analysis, only definite cases of FH using either criteria were referred for genetic testing. Additional detail on this can be found above Table 38.

A scenario analysis was conducted with an additional strategy where all people with high cholesterol were identified and put onto statins regardless of their FH status or genetic testing to isolate the incremental benefit of simply ensuring anyone with high cholesterol is appropriately treated with high-intensity statins.

Futema et al. (2015) provided alternative thresholds for primary care case identification and the proportion of people that require further investigation and prevalence associated with those alternative thresholds. The second threshold option (the first being the base case of total cholesterol greater than 9.3 mmol/L) was to exclude people with triglyceride levels above 2.3 mmol/L as these people are unlikely to have FH, enhancing the accuracy of the primary care database search.

Table 51: Primary care search criteria at alternative thresholds

Search algorithm	Proportion requiring further investigation	Prevalence of mutation positive FH in this proportion	Notes
Futema 2015 TC >9.3 (base case)	0.51%	28.00%	Includes people with triglycerides > 2.3 mmol/L
Futema 2015 TC >9.3 & TG <2.3	0.35%	41.18%	Excludes people with triglycerides > 2.3 mmol/L

O.3.6 Probabilistic sensitivity anlaysis

One way sensitivity analysis tests the robustness of results by varying one parameter at a time. Probabilistic sensitivity analysis tests the uncertainty in results by taking account of the joint uncertainty in several parameters at the same time by conducting Monte Carlo simulation. This is operationalised by establishing distributions around the means of these parameters. Sensitivity was correlated with specificity via Diagnostic Odds Ratios (DORs) rather than variance-covariance matrices as the clinical review did not identify enough data to power the latter. DORs were assumed to be fixed in the PSA rather than varied about their means.

The following clinical parameters were varied in the short term.

Table 52: PSA short term clinical parameters

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

The cost of genetic test was varied in PSA as follows.

Table 53: Genetic testing PSA parameters

Distribution	alpha	beta	Mean	se	Source
gamma	16.00	23.44	375	93.75	approximation
gamma	16.00	7.34	117.5	29.375	approximation

The 95% confidence intervals provided in the Simon Broome data were included as follows:

Table 54: Relative risk of CHD due to FH PSA parameters

Male	Mean RR	Lower CI	Upper CI	ln(RR)	se(ln(RR))
40	4.0028	2.83	5.49	1.386994	0.169044
45	4.0028	2.83	5.49	1.386994	0.169044
55	4.0028	2.83	5.49	1.386994	0.169044
65	1.6199	1.19	2.16	0.482364	0.15208
75	1.6199	1.19	2.16	0.482364	0.15208
85	1.6199	1.19	2.16	0.482364	0.15208
Female					
40	5.133	2.35	9.74	1.63569	0.362711
45	5.133	2.35	9.74	1.63569	0.362711

Male	Mean RR	Lower CI	Upper CI	ln(RR)	se(ln(RR))
55	5.133	2.35	9.74	1.63569	0.362711
65	2.2827	1.65	3.07	0.825359	0.158393
75	2.2827	1.65	3.07	0.825359	0.158393
85	2.2827	1.65	3.07	0.825359	0.158393

The uncertainty around long term costs and QALYs was established by taking the simulation output from the lipid modification model for a broadly representative set of age and sex subpopulations and using the maximum observed standard error as a percentage of the mean for these samples to represent a normal distribution around the deterministic estimates from the model. Different estimates were taken for costs and QALYs for the FH and polygenic cohorts to ensure differences in relative uncertainy were accounted for. Due to the tightness of the observed distributions, the simplicity of this methodology (versus one that ran probabilistic sensitivity analysis for every single sub population and then averaged the results) was not expected to affect any conclusions drawn from the model.

Table 55: Maximum SEs for Payoffs relative to the mean values

	Max se as a % of mean Costs	Max se as a % of mean QALYs
Polygenic	2.58%	1.05%
FH	5.44%	2.50%

O.4 Results

The identification and diagnosis decision tree module calculated the proportion of each subgroup allocated to the long term modules. This was converted into the number of actual people allocated using the estimates of each subpopulation that come into contact with the interventions.

Under the base case settings of the model, the maximum number of people with FH that a perfectly sensitive strategy would have been able to diagnose was 43,963 (at 100% take up rates, sensitivity and specificity). This assumes a data availability rate of 31% in primary care, which crucially determines the number of people that are ‘able to be found’ by the case finding strategies and includes the relatives found through cascade testing strategies.

Strategy 1 (no intervention) assumed that 20% of these people would already be receiving treatment with statins for high cholesterol, whether they had a clinical diagnosis of FH or not. Based on the assumptions in the model, only about 4,000 of the current 18,000 people with a clinical diagnosis of FH would have a monogenic mutation if diagnosed definitively via genetic testing.

Cascade testing only, strategy 2, resulted in 2,355 relatives being diagnosed and treated, increasing the proportion of people with FH who were treated to 25%.

The primary care case identification strategies resulted in 6,100 people in primary care with FH being diagnosed along with over 2000 of their relatives. This equated to 37% of people with FH in the model being identified.

Due to the relatively small numbers of people with early MI, secondary care case identification strategies identified about 600 relatives with FH.

The maximum number of people identified and diagnosed with FH was achieved by Strategy 7, primary care and secondary care case identification with clinical assessment using the Simon Broome criteria in addition to cascade testing.

Table 50: Base case, number of people allocated to long term modules by subpopulation and strategy

	Treated FH	Untreated FH	Treated polygenic	Untreated polygenic
1. No cascade testing and no case identification				
Current clinical diagnosis of FH	4,136	-	13,864	-
Relatives of people with a current clinical diagnosis of FH	-	4,675	-	-
People identified by a primary care database search	2,922	12,217	7,513	31,416
Relatives of people identified by a primary care database search	-	17,109	-	-
People with early MI	1,363	-	103,470	-
Relatives of people with early MI	-	1,540	-	-
2. Cascade testing				
Current clinical diagnosis of FH	4,136	-	13,864	-
Relatives of people with a current clinical diagnosis of FH	2,355	2,320	-	-
People identified by a primary care database search	2,922	12,217	7,513	31,416
Relatives of people identified by a primary care database search	-	17,109	-	-
People with early MI	1,363	-	103,470	-
Relatives of people with early MI	-	1,540	-	-
3. Primary care case identification, clinical assessment with SB criteria				
Current clinical diagnosis of FH	4,136	-	13,864	-
Relatives of people with a current clinical diagnosis of FH	2,355	2,320	-	-
People identified by a primary care database search	6,102	9,037	15,691	23,239
Relatives of people identified by a primary care database search	2,374	14,736	-	-
People with early MI	1,363	-	103,470	-
Relatives of people with early MI	-	1,540	-	-
4. Primary care case identification, clinical assessment with DLCN criteria				
Current clinical diagnosis of FH	4,136	-	13,864	-
Relatives of people with a current clinical diagnosis of FH	2,355	2,320	-	-
People identified by a primary care database search	6,102	9,037	15,691	23,239

	Treated FH	Untreated FH	Treated polygenic	Untreated polygenic
Relatives of people identified by a primary care database search	2,297	14,813	-	-
People with early MI	1,363	-	103,470	-
Relatives of people with early MI	-	1,540	-	-
5. Secondary care case identification, clinical assessment with SB criteria				
Current clinical diagnosis of FH	4,136	-	13,864	-
Relatives of people with a current clinical diagnosis of FH	2,355	2,320	-	-
People identified by a primary care database search	2,922	12,217	7,513	31,416
Relatives of people identified by a primary care database search	-	17,109	-	-
People with early MI	1,363	-	103,470	-
Relatives of people with early MI	595	945	-	-
6. Secondary care case identification, clinical assessment with DLCN criteria				
Current clinical diagnosis of FH	4,136	-	13,864	-
Relatives of people with a current clinical diagnosis of FH	2,355	2,320	-	-
People identified by a primary care database search	2,922	12,217	7,513	31,416
Relatives of people identified by a primary care database search	-	17,109	-	-
People with early MI	1,363	-	103,470	-
Relatives of people with early MI	576	964	-	-
7. Primary care and secondary care case identification with SB criteria				
Current clinical diagnosis of FH	4,136	-	13,864	-
Relatives of people with a current clinical diagnosis of FH	2,355	2,320	-	-
People identified by a primary care database search	6,102	9,037	15,691	23,239
Relatives of people identified by a primary care database search	2,374	14,736	-	-
People with early MI	1,363	-	103,470	-
Relatives of people with early MI	595	945	-	-
8. Primary care and secondary care case identification with DLCN criteria				

	Treated FH	Untreated FH	Treated polygenic	Untreated polygenic
Current clinical diagnosis of FH	4,136	-	13,864	-
Relatives of people with a current clinical diagnosis of FH	2,355	2,320	-	-
People identified by a primary care database search	6,102	9,037	15,691	23,239
Relatives of people identified by a primary care database search	2,297	14,813	-	-
People with early MI	1,363	-	103,470	-
Relatives of people with early MI	595	945	-	-

The overall results of the base case scenario produced when the proportion of people assigned to each module were combined with short term costs, long term costs and long term health benefits are reported in Table 49a. At a cost-effectivenes threshold of £20,000, Strategy 3, primary care case identification and clinical assessment with the Simon Broome criteria (in addition to cascade testing), was the most cost-effective strategy with the highest net monetary benefit. Table 58reports these results in terms of incremental analysis. Strategy 3 was the most cost-effective strategy because it had the highest incremental cost-effectiveness ratio up to the threshold of £20,000 per QALY.

Table 51: Base case results, ranked by NMB, £20,000/QALY threshold

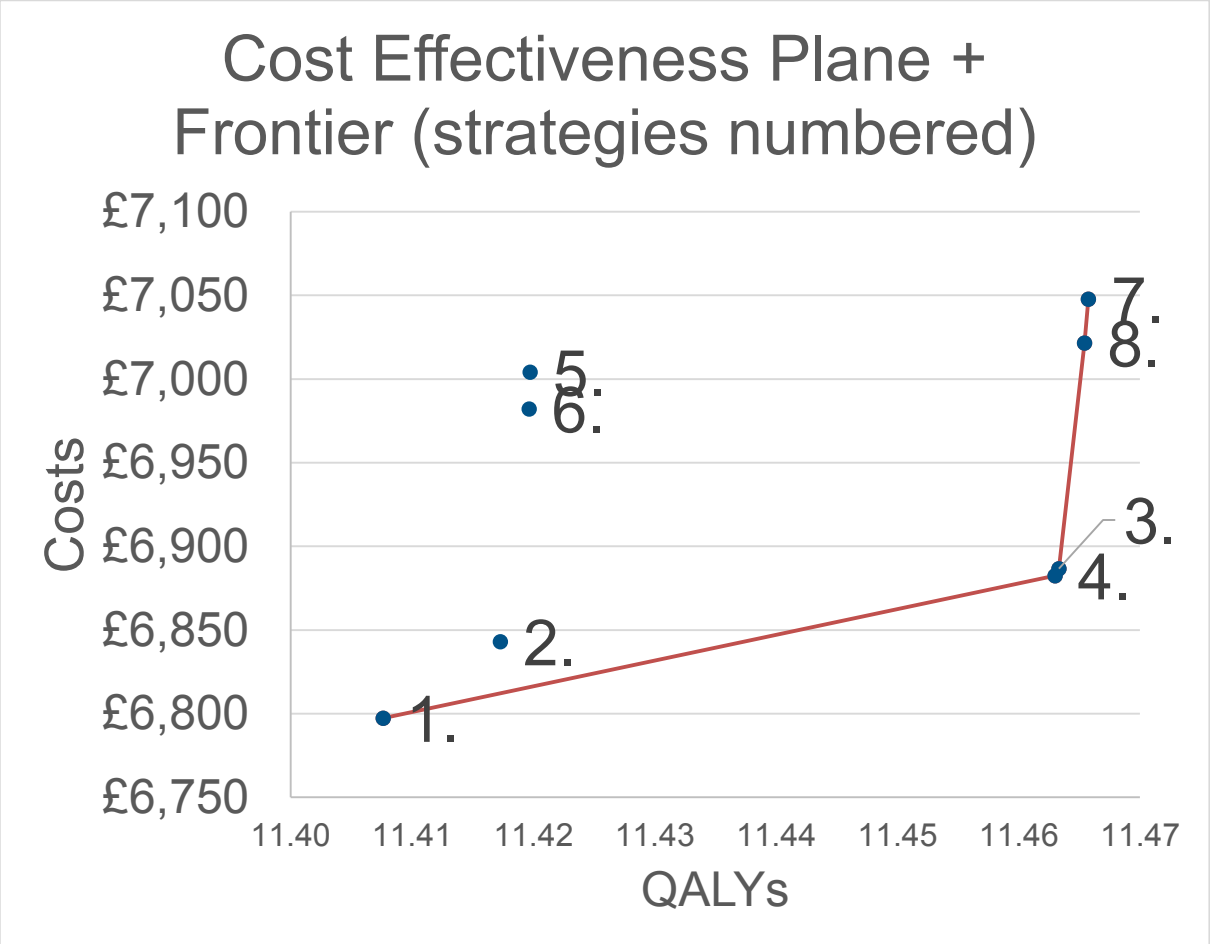
Strategy	Cost	QALYs	NMB	Rank
1. No cascade testing and no case identification	£6,797.26	11.408	221,355	8
2. Cascade testing	£6,843.03	11.417	221,503	5
3. Primary care case identification, clinical assessment with SB criteria	£6,886.65	11.463	222,379	1
4. Primary care case identification, clinical assessment with DLCN criteria	£6,882.41	11.463	222,377	2
5. Secondary care case identification, clinical assessment with SB criteria	£7,004.05	11.420	221,391	7
6. Secondary care case identification, clinical assessment with DLCN criteria	£6,982.19	11.420	221,411	6
7. Primary and secondary care case identification, clinical assessment with SB criteria	£7,047.67	11.466	222,267	4
8. Primary and secondary care case identification, clinical assessment with DLCN criteria	£7,021.53	11.465	222,287	3

Table 52: Incremental base case results

Strategy	Cost	QALYs	ICER
1. No cascade testing and no case identification	£6,797	11.408	£0
2. Cascade testing	£6,843	11.417	Ext.Dom
4. Primary care case identification, clinical assessment with DLCN criteria	£6,882	11.463	£1,538
3. Primary care case identification, clinical assessment with SB criteria	£6,887	11.463	£13,361
6. Secondary care case identification, clinical assessment with DLCN criteria	£6,982	11.420	Dominated
5. Secondary care case identification, clinical assessment with SB criteria	£7,004	11.420	Dominated
8. Primary and secondary care case identification, clinical assessment with DLCN criteria	£7,022	11.465	£63,492
7. Primary and secondary care case identification, clinical assessment with SB criteria	£7,048	11.466	£82,374

Strategy 3 had an ICER of £13,361/QALY compared with strategy 4, which was associated with an ICER of £1,538 vs no genetic testing although the differences in costs and QALYs between strategies 3 and 4 were very small. Strategies 7 and 8 had an ICERs well above the threshold usually considered cost effective by NICE.

Figure 13: Base case, cost-effectiveness plane



O.4.1 Base case, total short term economic cost

The total short term economic cost is reported in Table 59. The table below reports short term opportunity cost only. It does not report long term treatment costs or, more importantly, health benefits gained over the lifetime of people who are properly diagnosed and treated. Long term costs were dependent on the assumptions underpinning the distribution of risk scores and age groups in the target populations and very small in net terms due to cost savings associated with the effectiveness of treating FH and polygenic hypercholesterolaemia. The short term cost has therefore been presented alone to allow comparisons of the main differences between the proposed strategies including where the resource impact is likely to fall.

Table 53: Total short term economic cost by setting, strategy and subpopulation

Summary table for report - short term costs only			
Strategy/subpopulation	Cost to primary care	Cost to secondary care	Cost of genetic testing
1. No cascade testing and no case identification	-	-	-
Current clinical diagnosis of FH	-	-	-
Relatives of people with a current clinical diagnosis of FH	-	-	-
People identified by a primary care database search	-	-	-
Relatives of people identified by a primary care database search	-	-	-
People with early MI	-	-	-
Relatives of people with early MI	-	-	-
Total	£0	£0	£0
2. Cascade testing			
Current clinical diagnosis of FH	£0	£3,707,181	£5,676,750
Relatives of people with a current clinical diagnosis of FH	£0	£1,212,909	£543,636
People identified by a primary care database search	£0	£0	£0
Relatives of people identified by a primary care database search	£0	£0	£0
People with early MI	£0	£0	£0
Relatives of people with early MI	£0	£0	£0
Total	£0	£4,920,090	£6,220,386
3. Primary care case identification, clinical assessment with SB criteria			
Current clinical diagnosis of FH	£0	£3,707,181	£5,676,750
Relatives of people with a current clinical diagnosis of FH	£0	£1,212,909	£543,636
People identified by a primary care database search	£2,446,238	£2,832,836	£4,024,651
Relatives of people identified by a primary care database search	£0	£1,222,871	£548,101
People with early MI	£0	£0	£0
Relatives of people with early MI	£0	£0	£0
Total	£2,446,238	£8,975,796	£10,793,137
4. Primary care case identification, clinical assessment with DLCN criteria			

Summary table for report - short term costs only			
Current clinical diagnosis of FH	£0	£3,707,181	£5,676,750
Relatives of people with a current clinical diagnosis of FH	£0	£1,212,909	£543,636
People identified by a primary care database search	£2,606,800	£2,443,471	£3,335,790
Relatives of people identified by a primary care database search	£0	£1,222,871	£530,241
People with early MI	£0	£0	£0
Relatives of people with early MI	£0	£0	£0
Total	£2,606,800	£8,586,431	£10,086,417
5. Secondary care case identification, clinical assessment with SB criteria			
Current clinical diagnosis of FH	£0	£3,707,181	£5,676,750
Relatives of people with a current clinical diagnosis of FH	£0	£1,212,909	£543,636
People identified by a primary care database search	£0	£0	£0
Relatives of people identified by a primary care database search	£0	£0	£0
People with early MI	£0	£15,245,282	£20,387,178
Relatives of people with early MI	£0	£333,945	£137,423
Total	£0	£20,499,317	£26,744,987
6. Secondary care case identification, clinical assessment with DLCN criteria			
Current clinical diagnosis of FH	£0	£3,707,181	£5,676,750
Relatives of people with a current clinical diagnosis of FH	£0	£1,212,909	£543,636
People identified by a primary care database search	£0	£0	£0
Relatives of people identified by a primary care database search	£0	£0	£0
People with early MI	£0	£15,175,875	£15,594,160
Relatives of people with early MI	£0	£333,945	£132,945
Total	£0	£20,429,910	£21,947,491
7. Primary care and secondary care case identification with SB criteria			
Current clinical diagnosis of FH	£0	£3,707,181	£5,676,750
Relatives of people with a current clinical diagnosis of FH	£0	£1,212,909	£543,636
People identified by a primary care database search	£2,446,238	£2,832,836	£4,024,651
Relatives of people identified by a primary care database search	£0	£1,222,871	£548,101
People with early MI	£0	£15,245,282	£20,387,178
Relatives of people with early MI	£0	£333,945	£137,423
Total	£2,446,238	£24,555,023	£31,317,738
8. Primary care and secondary care case identification with DLCN criteria			
Current clinical diagnosis of FH	£0	£3,707,181	£5,676,750
Relatives of people with a current clinical diagnosis of FH	£0	£1,212,909	£543,636

Summary table for report - short term costs only			
People identified by a primary care database search	£2,606,800	£2,443,471	£3,335,790
Relatives of people identified by a primary care database search	£0	£1,222,871	£530,241
People with early MI	£0	£15,175,875	£15,594,160
Relatives of people with early MI	£0	£333,945	£132,945
Total	£2,606,800	£24,096,251	£25,813,523

The low specificities of clinical assessment tools result in people being referred for genetic testing even they they do not have FH. Table 60 reports the number of tests this resulted in for the entire population of England and Wales and the cost associated with this based on the base case median cost of genetic testing. The fourth and fifth columns encapsulate all other genetic testing (true positive clinical assessments, cascade testing for relatives that do and do not have FH). This table contains no information on the long term costs and health benefits of correctly diagnosing and treating people with FH or polygenic hypercholesterolaemia.

Table 54: Base case, cost of genetic testing for false positive clinical assessments vs. others

1. No cascade testing and no case identification				
Current clinical diagnosis of FH	0	£0	0	£0
Relatives of people with a current clinical diagnosis of FH	0	£0	0	£0
People identified by a primary care database search	0	£0	0	£0
Relatives of people identified by a primary care database search	0	£0	0	£0
People with early MI	0	£0	0	£0
Relatives of people with early MI	0	£0	0	£0
Total	0	£0	0	£0
2. Cascade testing				
Current clinical diagnosis of FH	0	£0	15,138	£5,676,750
Relatives of people with a current clinical diagnosis of FH	0	£0	4,627	£543,636
People identified by a primary care database search	0	£0	0	£0
Relatives of people identified by a primary care database search	0	£0	0	£0
People with early MI	0	£0	0	£0
Relatives of people with early MI	0	£0	0	£0
Total	0	£0	19,765	£6,220,386
3. Primary care case identification, clinical assessment with SB criteria				
Current clinical diagnosis of FH	0	£0	15,138	£5,676,750
Relatives of people with a current clinical diagnosis of FH	0	£0	4,627	£543,636

1. No cascade testing and no case identification				
People identified by a primary care database search	7,225	£2,709,419	3,507	£1,315,232
Relatives of people identified by a primary care database search	0	£0	4,665	£548,101
People with early MI	0	£0	0	£0
Relatives of people with early MI	0	£0	0	£0
Total	7,225	£2,709,419	27,937	£8,083,718
4. Primary care case identification, clinical assessment with DLCN criteria				
Current clinical diagnosis of FH	0	£0	15,138	£5,676,750
Relatives of people with a current clinical diagnosis of FH	0	£0	4,627	£543,636
People identified by a primary care database search	5,502	£2,063,415	3,393	£1,272,376
Relatives of people identified by a primary care database search	0	£0	4,513	£530,241
People with early MI	0	£0	0	£0
Relatives of people with early MI	0	£0	0	£0
Total	5,502	£2,063,415	27,670	£8,023,003
5. Secondary care case identification, clinical assessment with SB criteria				
Current clinical diagnosis of FH	0	£0	15,138	£5,676,750
Relatives of people with a current clinical diagnosis of FH	0	£0	4,627	£543,636
People identified by a primary care database search	0	£0	0	£0
Relatives of people identified by a primary care database search	0	£0	0	£0
People with early MI	53,486	£20,057,415	879	£329,763
Relatives of people with early MI	0	£0	1,170	£137,423
Total	53,486	£20,057,415	21,814	£6,687,572
6. Secondary care case identification, clinical assessment with DLCN criteria				
Current clinical diagnosis of FH	0	£0	15,138	£5,676,750
Relatives of people with a current clinical diagnosis of FH	0	£0	4,627	£543,636
People identified by a primary care database search	0	£0	0	£0
Relatives of people identified by a primary care database search	0	£0	0	£0
People with early MI	40,734	£15,275,142	851	£319,018
Relatives of people with early MI	0	£0	1,131	£132,945

1. No cascade testing and no case identification				
Total	40,734	£15,275,142	21,747	£6,672,349
7. Primary care and secondary care case identification with SB criteria				
Current clinical diagnosis of FH	0	£0	15,138	£5,676,750
Relatives of people with a current clinical diagnosis of FH	0	£0	4,627	£543,636
People identified by a primary care database search	7,225	£2,709,419	3,507	£1,315,232
Relatives of people identified by a primary care database search	0	£0	4,665	£548,101
People with early MI	53,486	£20,057,415	879	£329,763
Relatives of people with early MI	0	£0	1,170	£137,423
Total	60,712	£22,766,834	29,986	£8,550,904
8. Primary care and secondary care case identification with DLCN criteria				
Current clinical diagnosis of FH	0	£0	15,138	£5,676,750
Relatives of people with a current clinical diagnosis of FH	0	£0	4,627	£543,636
People identified by a primary care database search	5,502	£2,063,415	3,393	£1,272,376
Relatives of people identified by a primary care database search	0	£0	4,513	£530,241
People with early MI	40,734	£15,275,142	851	£319,018
Relatives of people with early MI	0	£0	1,131	£132,945
Total	46,236	£17,338,557	29,653	£8,474,966

O.4.2 One way sensitivity analysis

The results of the one way sensitivity analysis are reported in terms of rank based on net monetary benefit because of the large number of strategies and parameters varied as a simplified method of identifying when results change. The results are grouped as follows:

- Prevalence of FH
- Take up of interventions
- Number of relatives and cost of genetic testing
- Entire population assigned specific QRISK scores rather than spread evenly across scores

All rankings are based on deterministic net monetary benefit using a cost-effectiveness threshold of £20,000 per QALY, where rank 1 is the most cost effective strategy. A discussion of the results appears below the tables.

Table 55: One way sensitivity analysis, prevalence of FH

	Base Case Analysis	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	8	8	8
2. Cascade testing	5	5	5	5	5	5	7
3. Primary care case identification, clinical assessment with SB criteria	1	1	1	2	1	1	3
4. Primary care case identification, clinical assessment with DLCN criteria	2	2	2	1	2	2	4
5. Secondary care case identification, clinical assessment with SB criteria	7	7	7	7	7	7	6
6. Secondary care case identification, clinical assessment with DLCN criteria	6	6	6	6	6	6	5
7. Primary and secondary care case identification, clinical assessment with SB criteria	4	4	4	4	4	4	2
8. Primary and secondary care case identification, clinical assessment with DLCN criteria	3	3	3	3	3	3	1

Table 56: One way sensitivity analysis, take up of interventions

	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

Table 57: One way sensitivity analysis, number of relatives and cost of genetic testing

	Base Case Analysis	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	8	6	8	8	7
2. Cascade testing	5	5	7	5	5
3. Primary care case identification, clinical assessment with SB criteria	1	2	3	1	1
4. Primary care case identification, clinical assessment with DLCN criteria	2	1	4	2	2
5. Secondary care case identification, clinical assessment with SB criteria	7	8	6	7	8
6. Secondary care case identification, clinical assessment with DLCN criteria	6	7	5	6	6
7. Primary and secondary care case identification, clinical assessment with SB criteria	4	4	1	4	4
8. Primary and secondary care case identification, clinical assessment with DLCN criteria	3	3	2	3	3

Table 58: One way sensitivity analysis, alternative QRISK scores

	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

	Proportion assigned to risk bands		
8. Primary and secondary care case identification, clinical assessment with DLCN criteria	3	3	3

Discussion of one-way sensitivity analysis

When the prevalence of FH in people identified for further investigation in primary care was decreased to 20%, strategy 4, primary care case identification with clinical assessment using the DLCN criteria, became the most cost-effective strategy, with strategy 3 ranked second. Some exploratory threshold analysis was also conducted on this parameter and found that the prevalence of FH in the target group would have to decrease to 3.2% before primary care case-finding became cost-ineffective. There is no good reason to believe that the true value would be this low but this is also not hard evidence for a more inclusive case-finding strategy; it should be noted that low prevalence values in the target group would likely mean that such a strategy would not be robust to additional deterministic sensitivity analysis.

When the prevalence of FH in people with early MI was increased to an upper estimate of 8.3%, strategy 8, primary care and secondary care case identification with clinical assessment using the DLCN criteria, became the most cost-effective strategy. This was because a higher prevalence of FH in this subpopulation increased the yield of interventions designed to identify new cases in the secondary care setting. However, the upper estimate of 8.3% was based on a study where diagnosis was based on clinical assessment alone (De Backer 2015). This contrasts with the base case of 1.3% which was based on genetic diagnosis (Wald 2015), a more certain estimate of the prevalence of FH in this population. Strategy 3 was 3rd placed in terms of net monetary benefit when the prevalence of FH in people with early MI was 8.3%. The threshold at which strategy 3 no longer had the maximum net monetary benefit at a £20,000 per QALY threshold was ~3.8%. That is, the prevalence of FH in people with early MI had to be over 3.8% for the conclusions of the model to change.

A number of additional parameters were varied separately to those above:

- When the proportion of people in primary care databases for who data is available was increased to 100% from the base case of 31%, strategy 3 remained the most cost-effective option, although this has the expected consequence of very directly affecting the short term resource impact.
- The proportion of people already taking high intensity statins was varied from 10% to 99% and made no difference to the order of preferred strategies.
- The SB and DLCN referral algorithms were varied to their ‘definite only’ criteria but this resulted in lower net monetary benefits than the more inclusive criteria.

Strategies 7 and 8 became preferred in the high scenario analysis for the number of relatives approached. Threshold analysis reveals that the preferred strategies change once 8 relatives are identified and contacted per index case. This is 3.5x the base case value.

Overall, strategy 3 remained cost effective in most sensitivity analyses. Where results changed, primary care case identification was still often considered the most cost-effective intervention, but using the DLCN criteria for clinical assessment was preferred. Strategy 3 consistently had the second-highest net monetary benefit when results changed. The results were robust to changes in the cost of genetic testing, and changes in most of the take up rates. The prevalence of FH within MI was the most notable exception to these trends.

O.4.3 Detailed scenario analysis: Strategy 9, ensure everyone with high cholesterol in primary care are treated with lipid modification regardless of FH status (no genetic testing)

An additional scenario was requested during internal quality assurance. Much of the health benefit produced by these interventions was due to the polygenic population with high cholesterol invited for further assessment and receiving appropriate treatment. Therefore, an additional strategy was requested that retained cascade testing for the relatives of people

with a current clinical diagnosis of FH, but only included searching primary care databases for people with high cholesterol and prescribing appropriate cases high-intensity statins with no genetic testing for them or their relatives, thereby isolating the incremental costs and benefits of simply prescribing people with high cholesterol lipid modification treatment regardless of whether they have FH or not. The impact of this group is reduced with higher total cholesterol thresholds for primary care database searching.

Under this scenario, strategy 9 ranked well, with a very low incremental cost-effectiveness ratio, but strategy 3 remained the most cost-effective due to the additional health benefit of diagnosing relatives through genetic cascade testing.

Total short term economic costs are provided for strategy 9 along with all other strategies in Table 67. It reflects the low cost of reviewing people with high cholesterol in primary care, albeit at the exclusion of assessment with one of the FH clinical tools. The costs that appear for secondary care and genetic testing are identical to strategy 2, due to the cascade testing from currently diagnosied index cases included in this strategy.

Figure 14: Sensitivity analysis, strategy 9, structure of pathway

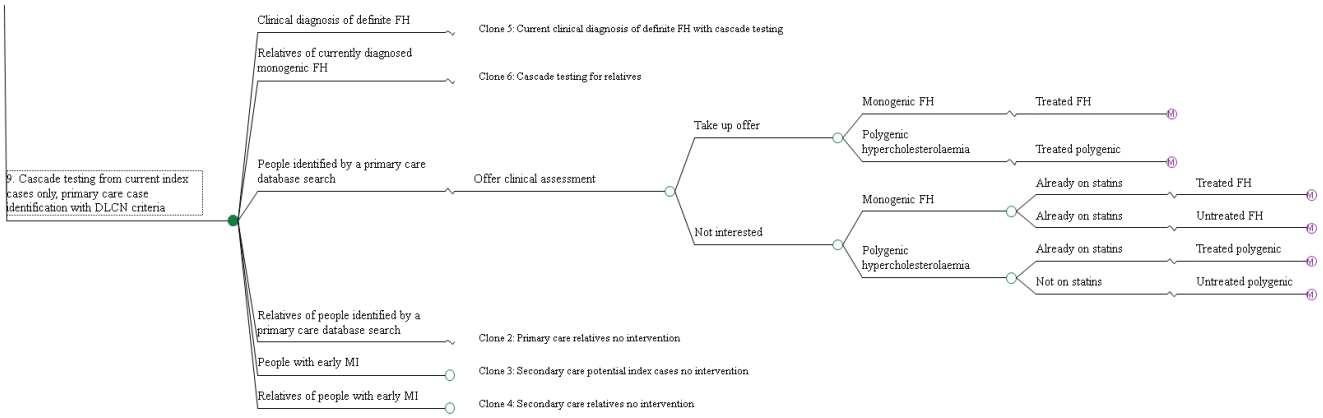


Table 59: Sensitivity analysis, strategy 9, results ranked by net monetary benefit

Strategy	Cost	QALYs	NMB	Rank
3. Primary care case identification, clinical assessment with SB criteria	£6,886.65	11.463	222,379	1
4. Primary care case identification, clinical assessment with DLCN criteria	£6,882.41	11.463	222,377	2
8. Primary and secondary care case identification, clinical assessment with DLCN criteria	£7,021.53	11.465	222,287	3
7. Primary and secondary care case identification, clinical assessment with SB criteria	£7,047.67	11.466	222,267	4
9. Primary care case identification, no cascade testing from new index cases	£6,851.76	11.454	222,220	5
2. Cascade testing	£6,843.03	11.417	221,503	6
6. Secondary care case identification, clinical assessment with DLCN criteria	£6,982.19	11.420	221,411	7
5. Secondary care case identification, clinical assessment with SB criteria	£7,004.05	11.420	221,391	8
1. No cascade testing and no case identification	£6,797.26	11.408	221,355	9

Table 60: Sensitivity analysis, strategy 9, incremental analysis

Strategy	Cost	QALYs	ICER
1. No cascade testing and no case identification	6797.257	11.40763	£0
2. Cascade testing	6843.03	11.41729	Ext.Dom
9. Primary care case identification, no cascade testing from new index cases	6851.76	11.45357	£1,186
4. Primary care case identification, clinical assessment with DLCN criteria	6882.41	11.46299	£3,253
3. Primary care case identification, clinical assessment with SB criteria	6886.649	11.4633	£13,361
6. Secondary care case identification, clinical assessment with DLCN criteria	6982.186	11.41965	Dominated
5. Secondary care case identification, clinical assessment with SB criteria	7004.05	11.41973	Dominated
8. Primary and secondary care case identification, clinical assessment with DLCN criteria	7021.53	11.46543	£63,492
7. Primary and secondary care case identification, clinical assessment with SB criteria	7047.67	11.46575	£82,374

Table 61: Summary total short term economic cost, detailed scenario analysis with strategy 9

Total short term economic cost									
Strategy	Primary care	Secondary care	Genetic testing	Total short term cost	Number of unnecessary genetic tests	Cost of unnecessary genetic tests	Number of other genetic tests	Cost of other genetic tests	False negatives missed by clinical assessment
1. No cascade testing and no case identification	-	-	-	£0	0	£0	0	£0	0
2. Cascade testing	£0	£4,920,090	£6,220,386	£11,140,475	0	£0	19,765	£6,220,386	0
3. Primary care case identification, clinical assessment with SB criteria	£2,446,238	£8,975,796	£10,793,137	£22,215,171	7,225	£2,709,419	27,937	£8,083,718	1,665
4. Primary care case identification, clinical assessment with DLCN criteria	£2,606,800	£8,586,431	£10,086,417	£21,279,648	5,502	£2,063,415	27,670	£8,023,003	2,104
5. Secondary care case identification, clinical assessment with SB criteria	£0	£20,499,317	£26,744,987	£47,244,303	53,486	£20,057,415	21,814	£6,687,572	150
6. Secondary care case identification, clinical assessment with DLCN criteria	£0	£20,429,910	£21,947,491	£42,377,401	40,734	£15,275,142	21,747	£6,672,349	189
7. Primary and secondary care case identification, clinical assessment with SB criteria	£2,446,238	£24,555,023	£31,317,738	£58,318,999	60,712	£22,766,834	29,986	£8,550,904	1,815
8. Primary and secondary care case identification, clinical assessment with DLCN criteria	£2,606,800	£24,096,251	£25,813,523	£52,516,574	46,236	£17,338,557	29,653	£8,474,966	2,294
9. Primary care case identification, no cascade testing from new index cases	£2,350,712	£4,920,090	£6,220,386	£13,491,187	0	£0	19,765	£6,220,386	0

O.4.4 Detailed scenario analysis: 'Definite' clinical assessments only referred for genetic testing

As explained in section O.3.5, only referring people with definite FH based on clinical assessment ensures that the genetic testing resources are focussed on people most likely to have FH. The goal of this scenario analysis was to establish whether the cost savings achieved by the definite strategies were worth the health benefits lost due to the increase in false negative clinical assessments.

Under this scenario, the strategies based on referral of definite FH cases only ranked well with low ICERs but strategy 4, primary care case identification and clinical assessment using the DLCN criteria, was the most cost-effective strategy with an ICER of £3,987 per QALY (Table 68). The committee noted that due to the uniform assumption that clinical assessment would be done by a specialist nurse, when in reality the level of training needed to assess the 'definite' criteria would be higher, may have undervalued the benefit of the 'rule out' strategies over the 'rule in' ones. This limitation did not affect the conclusions of the model as it favoured the diagnostic criteria that were already shown to be more cost effective.

The total short term economic cost for all strategies was reduced by roughly a quarter under this scenario (Table 69).

Table 62: Sensitivity analysis, definite vs. probable referral criteria, ranked by Net Monetary Benefit (NMB), deterministic

Strategy	Costs	QALYs	NMB
Prob 3.	£6,887	11.4633	£222,379
Prob 4.	£6,882	11.4630	£222,377
Def 4.	£6,867	11.4598	£222,328
Def 3.	£6,858	11.4575	£222,292
Prob 8.	£7,022	11.4654	£222,287
Def 7.	£6,890	11.4585	£222,280
Def 8.	£6,938	11.4608	£222,277
Prob 7.	£7,048	11.4657	£222,267
9.	£6,852	11.4536	£222,220
2.	£6,843	11.4173	£221,503
Def 5.	£6,875	11.4183	£221,490
Def 6.	£6,914	11.4188	£221,463
Prob 6.	£6,982	11.4197	£221,411
Prob 5.	£7,004	11.4197	£221,391
1.	£6,797	11.4076	£221,355

Strategies based on referring possible and definite Simon Broome and probable and definite DLCN results marked with "Prob" in strategy number. Strategies based on referring definite Simon Broome and definite DLCN indicated with a "Def" in the strategy name.

Table 63: Summary total economic cost, all strategies definite referral criteria only

Total short term economic cost									
Strategy	Primary care	Secondary care	Genetic testing	Total short term cost	Number of unnecessary genetic tests	Cost of unnecessary genetic tests	Number of other genetic tests	Cost of other genetic tests	False negatives missed by clinical assessment
1. No cascade testing and no case identification	-	-	-	£0	0	£0	0	£0	0
2. Cascade testing	£0	£4,920,090	£6,220,386	£11,140,475	0	£0	19,765	£6,220,386	0
3. Primary care case identification, clinical assessment with SB criteria	£1,956,541	£6,098,306	£7,202,095	£15,256,943	608	£228,002	23,070	£6,974,093	9,689
4. Primary care case identification, clinical assessment with DLCN criteria	£2,344,978	£6,700,846	£8,159,880	£17,205,704	2,006	£752,405	24,971	£7,407,475	6,555
5. Secondary care case identification, clinical assessment with SB criteria	£0	£10,308,758	£8,097,221	£18,405,979	4,501	£1,687,861	20,593	£6,409,360	872
6. Secondary care case identification, clinical assessment with DLCN criteria	£0	£14,946,650	£12,087,961	£27,034,611	14,853	£5,569,941	21,070	£6,518,020	590
7. Primary and secondary care case identification, clinical assessment with SB criteria	£1,956,541	£11,486,975	£9,078,930	£22,522,446	5,109	£1,915,863	23,899	£7,163,067	10,561
8. Primary and secondary care case identification, clinical assessment with DLCN criteria	£2,344,978	£16,727,406	£14,027,456	£33,099,840	16,860	£6,322,347	26,276	£7,705,109	7,145
9. Primary care case identification, no cascade testing from new index cases	£2,350,712	£4,920,090	£6,220,386	£13,491,187	0	£0	19,765	£6,220,386	0

O.4.5 Detailed scenario analysis: Alternative thresholds for searching primary care databases

We considered configuring the economic model to explicitly compare a variety of of database search criteria, such as the possible TC>8.6 and TG<2.3 discussed in Futema et a 2015 and those discussed in section O.3.1 above but decided that the evidence underpinning these criteria would not be strong enough to justify the resource impact that would result from any positive recommendations that might arise. In the case of those criteria discussed in section O.3.1 this was either due to the implausibility of the implied total prevalence of FH or due to the unimplementability of having criteria too broad. It was felt that the estimated prevalence of FH in lower TC thesholds discussed in Futema et al was calculated from a trend drawn from too few individuals to be robust.

The Futema criteria of TC>9.3 and TG<2.3, within which the prevalence of FH was confirmed by genetic testing, would obviously be cost-effective compared to TC>9.3 only as all the individuals identified in the study had TG<2.3. If these data can be believed then all individuals with a TC>9.3 who have FH would have TG<2.3. Due to small numbers in the study, we asked the committee for clinical opinion on which of these criteria should be used in the base case analysis. The ranking of strategies does not change under these assumptions but the overall resource impact decreases as expected.

Table 64: Incremental results, scenario analysis, primary care search total cholesterol > 9.3 mmol/L & triglycerides < 2.3 mmol/L

Incremental Results (incl Strategy 9)			
Strategy	Costs	QALYs	ICER
1. No cascade testing and no case identification	£6,813	11.428	£0
2. Cascade testing	£6,865	11.439	Ext.Dom
9. Primary care case identification, no cascade testing from new index cases	£6,869	11.464	£1,548
4. Primary care case identification, clinical assessment with DLCN criteria	£6,893	11.473	£2,696
3. Primary care case identification, clinical assessment with SB criteria	£6,896	11.474	£7,720
6. Secondary care case identification, clinical assessment with DLCN criteria	£7,025	11.442	Dominated
5. Secondary care case identification, clinical assessment with SB criteria	£7,050	11.442	Dominated
8. Primary and secondary care case identification, clinical assessment with DLCN criteria	£7,053	11.476	£63,040
7. Primary and secondary care case identification, clinical assessment with SB criteria	£7,080	11.477	£89,554

Table 65: Total short term economic cost, scenario analysis, primary care search total cholesterol > 9.3 mmol/L & triglycerides < 2.3 mmol/L

Total short term economic cost									
Strategy	Primary care	Secondary care	Genetic testing	Total short term cost	Number of unnecessary genetic tests	Cost of unnecessary genetic tests	Number of other genetic tests	Cost of other genetic tests	False negatives missed by clinical assessment
1. No cascade testing and no case identification	-	-	-	£0	0	£0	0	£0	0
2. Cascade testing	£0	£4,920,090	£6,220,386	£11,140,475	0	£0	19,765	£6,220,386	0
3. Primary care case identification, clinical assessment with SB criteria	£1,663,419	£7,799,513	£9,061,223	£18,524,156	3,385	£1,269,419	26,656	£7,791,804	1,404
4. Primary care case identification, clinical assessment with DLCN criteria	£1,763,931	£7,600,115	£8,707,353	£18,071,399	2,578	£966,753	26,432	£7,740,600	1,775
5. Secondary care case identification, clinical assessment with SB criteria	£0	£20,499,317	£26,744,987	£47,244,303	53,486	£20,057,415	21,814	£6,687,572	150
6. Secondary care case identification, clinical assessment with DLCN criteria	£0	£20,429,910	£21,947,491	£42,377,401	40,734	£15,275,142	21,747	£6,672,349	189
7. Primary and secondary care case identification, clinical assessment with SB criteria	£1,663,419	£23,378,741	£29,585,824	£54,627,984	56,872	£21,326,834	28,705	£8,258,990	1,554
8. Primary and secondary care case identification, clinical assessment with DLCN criteria	£1,763,931	£23,109,935	£24,434,458	£49,308,325	43,312	£16,241,895	28,414	£8,192,563	1,964
9. Primary care case identification, no cascade testing from new index cases	£1,348,062	£4,920,090	£6,220,386	£12,488,537	0	£0	19,765	£6,220,386	0

Detailed scenario analysis: Alternative Relative Risks

The relative risk associated with FH over and above polygenic hypercholesterolaemia was uncertain. The Guideline Committee believed that the relative risks could be higher than those used in the base case analysis (the Simon Broome register data). They also believed that the relative treatment effect could be greater than in the polygenic population. Scenario analyses were therefore performed to investigate extreme changes in these parameters. The overall CVD risks associated with various types of patients within these scenario analyses are detailed in section O.3.4 above.

Table 66: ICERs of strategies under different scenario analyses

Strategy	Low RR		Strategy	High RR		Strategy	High RR + High Treatment Effect
1.	£0		1.	£0		1.	£0
2.	Ext.Dom		9.	£535		9.	£94
9.	£2,017		2.	Dominated		4.	£745
4.	£5,361		4.	£1,785		3.	£7,685
3.	£16,949		3.	£10,811		2.	Dominated
6.	Dominated		6.	Dominated		8.	£42,109
5.	Dominated		8.	£55,577		6.	Dominated
8.	£74,424		5.	Dominated		7.	£55,074
7.	£96,072		7.	£72,439		5.	Dominated

Table 66 shows that the ICERs move in the directions expected but the decision is insensitive to even the extreme variations in risk related parameters shown here. Furthermore, these risk profiles were then combined with the one-way sensitivity analyses detailed in section O.4.2. in multi-way sensitivity analyses and rankings of treatments were found not to materially alter.

O.4.6 Detailed scenario analysis: SAFEHEART Data

A study predicting risks in the general treated-FH population (Perez de Isla et al 2017) was highlighted by a stakeholder during consultation. This study was published after the cutoff date for searches and after any committee meetings where the design of the economic model developed for this guideline was discussed. It was not possible to configure the economic model to match the specific distribution of CVD events predicted by the SAFEHEART statistical model. This is mostly because the economic model structure was a cohort model and the correlation data necessary to predict cohort level effects were not available in the SAFEHEART paper. Nevertheless, we conducted a sensitivity analysis where we calibrated the long term module for the FH cohort to predict the overall 10-year risks reported in the SAFEHEART paper as closely as possible. The SAFEHEART data predict a 10-year CVD risk of 7.53% for patients with treated FH whereas the 10-year CVD risk in the guideline model ranged between 15%-44%.

Table 67: Adjusted risks calibrating treated-FH arm to SAFEHEART data

Statins	Base Effectiveness		High Effectiveness	
Patients	Untreated	Treated	Untreated	Treated
Male 40	20.1%	10.4%	17.7%	7.5%
Male 50	19.5%	10.4%	17.1%	7.5%
Female 40	17.5%	7.5%	20.9%	7.5%
Female 50	17.4%	7.5%	21.0%	7.5%

Table 67 shows that we were able to match the risks of the female cohort quite closely but were unable to reduce the male risks any further than 10.4% in the base case. This is because the risk equations used in the model would have begun to predict negative risks below this level. This is a limitation of this sensitivity analysis. Calibrating the treated-FH cohort in this way allowed the back-calculation of costs and QALYs for the untreated cohort (those who would have had a similar risk profile were it not for statin treatment). The results are in Table 68.

Table 68: Long Term Costs and QALYs for SAFEHEART calibrated cohorts

	M Cost	M QALYs	F Cost	F QALYs	T ICER M	T ICER F
Implied No Treatment	£7,217	14.93	£5,988	15.79		
Treatment	£9,822	15.67	£9,308	16.49	£3,537	£4,775
High Effectiveness Implied No Treatment	£6,648	15.23	£7,033	15.63		
High Effectiveness Treatment	£9,318	16.10	£9,384	16.62	£3,069	£2,379

Table 68 shows that under these assumptions it is not as cost effective to treat FH as under the base case assumptions (where it may have been cost saving). The resulting implications for the case finding strategies are shown in Table 69.

Table 69: Incremental cost-effectiveness ratios (SAFEHEART calibrated model)

Incremental Results (incl Strategy 9)			
Strategy	Costs	QALYs	ICER
1. No cascade testing and no case identification	£5,703	12.193	£0
2. Cascade testing	£5,784	12.201	Ext.Dom
9. Primary care case identification, no cascade testing from new index cases	£5,841	12.234	£3,367

Incremental Results (incl Strategy 9)			
4. Primary care case identification, clinical assessment with DLCN criteria	£5,906	12.241	£8,850
3. Primary care case identification, clinical assessment with SB criteria	£5,911	12.242	£21,749
6. Secondary care case identification, clinical assessment with DLCN criteria	£5,932	12.202	Dominated
5. Secondary care case identification, clinical assessment with SB criteria	£5,954	12.203	Dominated
8. Primary and secondary care case identification, clinical assessment with DLCN criteria	£6,054	12.243	£85,724
7. Primary and secondary care case identification, clinical assessment with SB criteria	£6,081	12.244	£109,820

These data suggest that primary care case finding with the DLCN remains cost effective but that primary care case finding with the SB may not be, with an ICER of £21.7k per QALY. This is because sensitivity is relatively less valuable than under the base case assumptions. When the upper effectiveness estimate for statin treatment is used, the results return to similar values to those under the base case. Primary care case finding remains cost effective when subjected to one-way sensitivity analysis even under the SAFEHEART assumptions.

Table 70: Incremental cost-effectiveness ratios (SAFEHEART Calibrated + high effectiveness of statins)

Incremental Results (incl Strategy 9)			
Strategy	Costs	QALYs	ICER
1. No cascade testing and no case identification	£5,732	12.214	£0
2. Cascade testing	£5,809	12.224	Ext.Dom
9. Primary care case identification, no cascade testing from new index cases	£5,859	12.261	£2,739
4. Primary care case identification, clinical assessment with DLCN criteria	£5,920	12.270	£6,333
3. Primary care case identification, clinical assessment with SB criteria	£5,925	12.271	£16,272
6. Secondary care case identification, clinical assessment with DLCN criteria	£5,956	12.227	Dominated
5. Secondary care case identification, clinical assessment with SB criteria	£5,978	12.227	Dominated
8. Primary and secondary care case identification, clinical assessment with DLCN criteria	£6,067	12.273	£65,568
7. Primary and secondary care case identification, clinical assessment with SB criteria	£6,094	12.273	£84,135

There are several reasons why these data should not be relied upon to concretely prefer the DLCN to the SB criteria:-

- The Guideline Committee believe that a diagnosis of FH is more effective than the mean estimate of statin treatment for people with polygenic hypercholesterolaemia and may even reduce risks down to normal population levels. In the high effectiveness sensitivity analysis, which does not take risks down this far, the results were largely unchanged.
- The population in the SAFEHEART study does not reflect the population in the case finding model as only the patients with the very highest cholesterol and therefore higher absolute risk will be found (plus their relatives, for whom the SAFEHEART data would likely be more representative).

- The results of the PSA (O.4.7) show that the confidence intervals of strategies 3 and 4 overlap almost exactly and the mean result only differs by £1 of NMB
- Unlike the base case analysis, the results produced by the model using the SAFEHEART data are dissimilar from other models evaluating the cost effectiveness of cascade testing, notably Kerr 2016. The use of the high-effectiveness data reduces the disparity.
- NICE's cost effectiveness threshold is £20-30k per QALY and the SB would be the most cost effective at the upper limit. This finding is robust to one-way sensitivity analysis.

O.4.7 Probabilistic sensitivity analysis (base case and SAFEHEART analysis)

Probabilistic sensitivity analysis indicated that strategy 3 had a 53.7% probability of being the most cost-effective option at a threshold of £20,000 per QALY. Strategy 4 had a 43.5% probability of being the most cost effective option (Table 72) although their confidence intervals overlapped almost exactly.

The cost-effectiveness acceptability curve is presented below. This shows the probability of selected strategies being cost effective at different thresholds relative to other selected thresholds. Four strategies were selected for this analysis based on their deterministic results. Strategy 9 had the highest probability of being cost effective up to a threshold ICER of ~£3,500/QALY, above which, primary care case finding became the most cost effective option. Strategy 4 has the highest probability of being cost effective between approximately £3,500 and £16,600 per QALY. Strategy 3 is more likely to be cost effective for thresholds greater than £16,600 per QALY.

Figure 15: Cost-effectiveness acceptability curve, base case assumptions

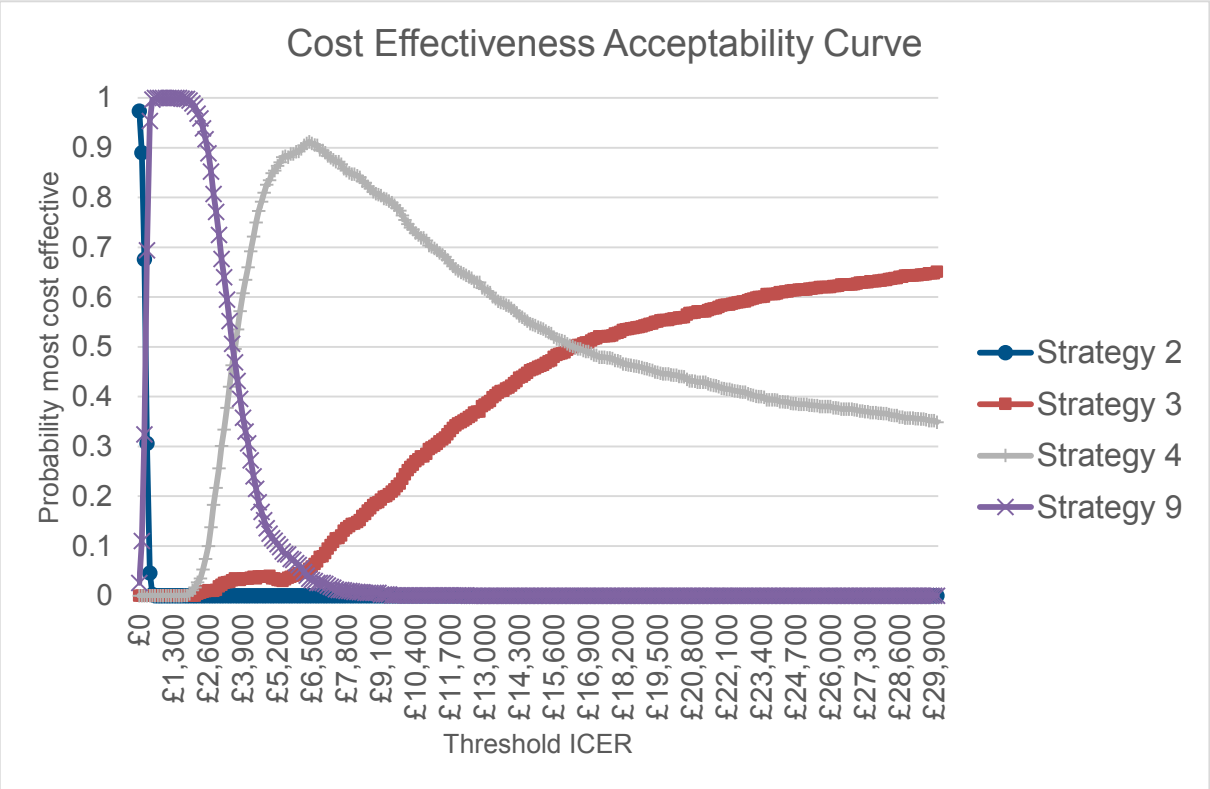


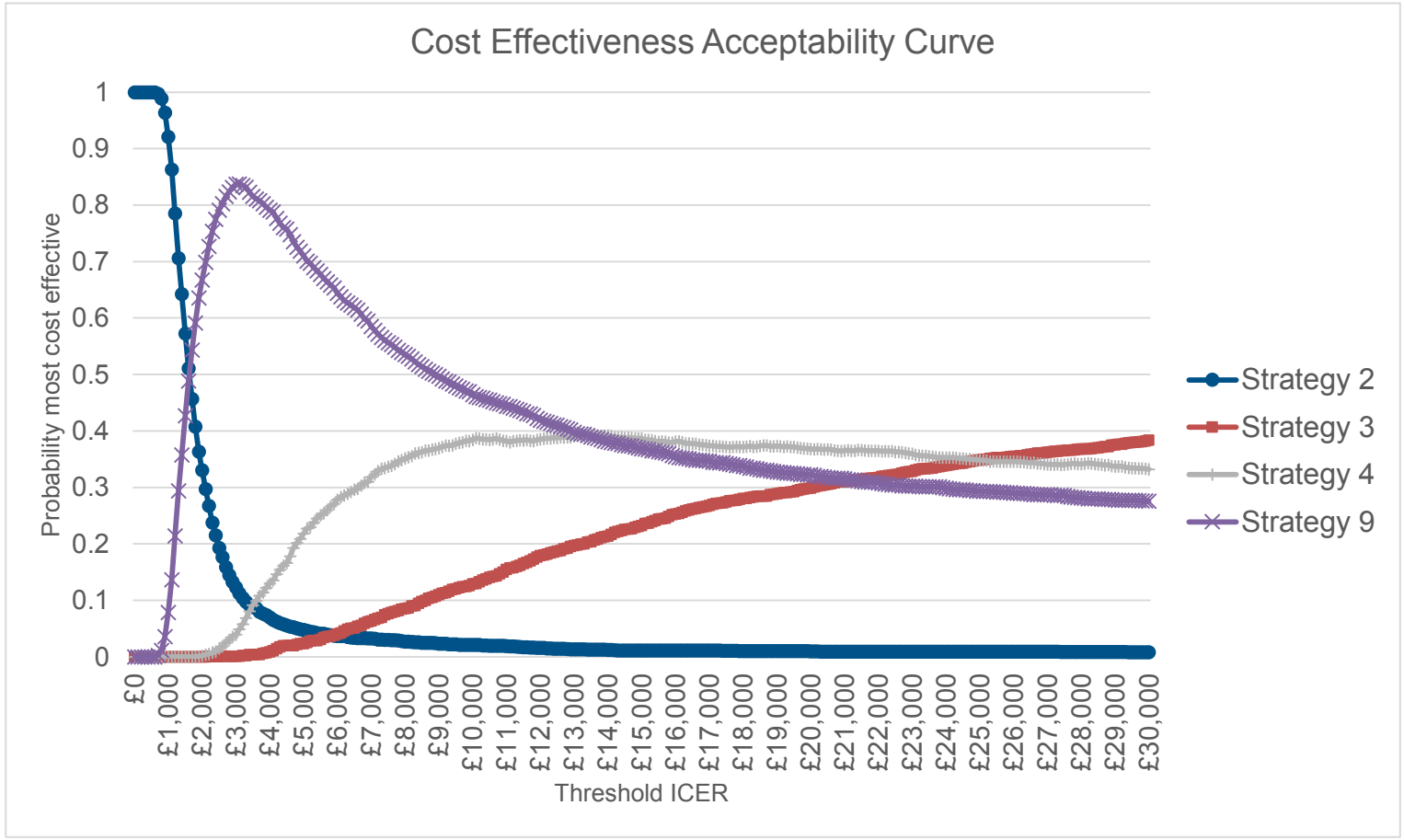
Table 71: Probabilistic results, base case

Strategy	NMB			Probability most cost effective
	Mean	Lower 95% CI	Upper 95% CI	
1. No cascade testing and no case identification	222,081	207,026	234,106	0.00%
2. Cascade testing	222,231	207,137	234,277	0.00%
3. Primary care case identification, clinical assessment with SB criteria	223,088	208,285	234,905	53.70%
4. Primary care case identification, clinical assessment with DLCN criteria	223,086	208,277	234,903	43.50%
5. Secondary care case identification, clinical assessment with SB criteria	222,117	207,024	234,125	0.00%
6. Secondary care case identification, clinical assessment with DLCN criteria	222,137	207,044	234,148	0.00%
7. Primary and secondary care case identification, clinical assessment with SB criteria	222,974	208,172	234,747	0.30%
8. Primary and secondary care case identification, clinical assessment with DLCN criteria	222,995	208,184	234,767	2.50%
9. Primary care case identification, no cascade testing from new index cases	222,935	208,004	234,822	0.00%

Table 72: Probabilistic results, SAFEHEART Analysis

Strategy	NMB			Probability most cost effective
	Mean	Lower 95% CI	Upper 95% CI	
1. No cascade testing and no case identification	238,442	229,895	245,108	9.80%
2. Cascade testing	238,508	230,117	245,137	0.00%
3. Primary care case identification, clinical assessment with SB criteria	239,188	231,134	245,711	31.48%
4. Primary care case identification, clinical assessment with DLCN criteria	239,189	231,123	245,712	55.12%
5. Secondary care case identification, clinical assessment with SB criteria	238,374	230,036	244,951	0.00%
6. Secondary care case identification, clinical assessment with DLCN criteria	238,394	230,044	244,955	0.00%
7. Primary and secondary care case identification, clinical assessment with SB criteria	239,054	231,034	245,559	0.48%
8. Primary and secondary care case identification, clinical assessment with DLCN criteria	239,075	231,059	245,586	3.12%
9. Primary care case identification, no cascade testing from new index cases	239,111	230,947	245,665	27.80%

Figure 16: Cost Effectiveness Acceptability Curve, SAFEHEART Analysis



O.5 Discussion

This analysis found that primary care case identification with clinical assessment using the Simon Broome criteria in addition to cascade testing was cost effective with an ICER of £13,361 per QALY and a 54% probability of being cost effective. Primary care case identification using the DLCN criteria had a 43% probability of being the most cost-effective strategy and deterministic costs and QALYs that were very close to the Simon Broome option. The main cost driver, accounting for around 50% of short term costs, was the increase in genetic tests.

These results were robust to the cost of genetic testing, the number of relatives approached for cascade testing and most take up rates. Where results changed, strategy 4, primary care case identification using the DLCN criteria for clinical assessment usually became the most cost-effective option, highlighting how close these two strategies were and how primary care case identification with either clinical assessment tool was likely to be a cost-effective intervention. This finding was supported by the probabilistic sensitivity analysis, where the confidence intervals around the NMB of either intervention overlapped almost exactly.

Primary care case identification remained cost effective when compared with a strategy of treating everyone with lipid modification regardless of their FH status and without genetic or cascade testing.

Referring both possible and definite cases of FH for genetic testing based on the Simon Broome criteria from primary care (strategy 3) remained cost effective compared with referring definite cases only, despite the short term cost savings offered by the latter.

It is possible that more accurate and/or cost-effective search criteria exist in the literature but could not be used to inform the model due to diagnosis of FH in the studies being based on clinical assessment rather than genetic testing, leaving the true prevalence of FH within these populations uncertain. Further research in this area has the potential to ensure primary care resources are focussed on those people most likely to have FH by establishing the accuracy of database search algorithms based on genetically confirmed diagnoses. This research could also be used to clarify which clinical assessment tool is the most appropriate for use in primary care in England and Wales.

There are a number of advantages to this analysis. It is the first time case identification in addition to cascade testing has been compared with cascade testing alone. In addition, a novel meta-analysis based on the latest data using genetic testing as the reference test, was used to inform a comparison of the two main clinical assessment tools, the Simon Broome criteria and DLCN criteria. Another advantage of this analysis is that the prevalence for each specific subpopulation was taken from recent, peer-reviewed literature. Long term impacts of treating FH and polygenic hypercholesterolaemia were based on the economic analysis conducted for the NICE lipid modification guideline.

Interpretation of these results needs to take into consideration that cost effectiveness of the primary care case identification strategies in this model was influenced by the number of people with polygenic hypercholesterolaemia that come into contact with primary care as a result of the interventions. Although the guideline is focused on familial hypercholesterolaemia, the committee took the view that the polygenic population would be impacted by the interventions and should continue to be included in the model.

This analysis confirmed the cost effectiveness of cascade testing compared with no cascade testing with an ICER of £4,740 per QALY and 100% likelihood the strategy is cost effective compared with no cascade testing at a threshold of £20,000 per QALY. However, additional health benefits are achieved at an acceptable cost with primary care case identification strategies. The ICER for cascade testing alone, although cost effective and comparable to

another recently published UK CUA, was greater than those reported by some other studies. This was potentially due to:

- the adoption of a stricter definition of FH in the present analysis based on LDLR, apoB or PCSK9 mutations;
- the proportion of people with a current clinical diagnosis of FH who actually have one of these mutations set at 23% based on the experiences of services in the UK;
- a conservative approach to the number of relatives approached for cascade testing based on the experiences of services in the UK set at 2.22 per index case; and
- inclusion of take up rates for both index cases and relatives (set at 84% and 60% respectively), limiting the effectiveness of cascade testing.

The analysis has a number of limitations, mainly related to the assumptions required to operationalise the model. Genetic testing was assumed to have perfect sensitivity and specificitya single probability of take up was used to represent take up across the entire care pathway, and all people were assumed to accept and adhere to lipid modification treatment once diagnosed. Assuming 100% accuracy in genetic testing was a limitation common to all strategies so was thought not to affect the overall conclusions of the model but was noted to marginally favour strategies implying the SB criteria due to undervaluing the costs of its lower specificity, which strengthened the committee's conclusions not to overinterpret the consistently higher rank of the SB over the DLCN criteria and recommend that either be used in practice. The assumptions related to statin use may have overestimated the cost effectiveness of all interventions compared with no case identification and no cascade testing, although given that ranking of the strategies was completely insensitive to the number of people already taking statins within the model, this limitiation was assessed as minor. The minimum starting age was 40 as this was the lowest used in the lipid modification model. This limitation likely led to an underestimation of the cost effectiveness of all strategies due to the increased risk of coronary heart disease at younger ages due to FH. There was uncertainty as to the true relative risk of CVD and relative treatment effect between people with and without FH among those with a total cholesterol of >9.3mmol/L, various theoretical data were tested in sensitivity analysis but did not affect conclusions. There were also no data to inform the distribution of risk scores in the target population but the rankings were insensitive to extreme high and low values so this limitation was considered minor. Another limitation is that crossover has not been accounted for. It is likely that an intervention of primary care case identification will identify people that have already been diagnosed with FH through cascade testing, and vice versa. However, no data was identified in the literature to inform the inclusion of this into the model.

O.6 Conclusion

The identification of FH by analysing primary care databases in addition to cascade testing is likely to be a cost effective strategy. The Simon Broome criteria is likely to be more cost-effective than the DLCN although the results for both clinical assessment tools are very close. Strategies that involve case identification in people with early MI are unlikely to be cost effective. The model confirmed that cascade testing (alone) is cost effective compared with no cascade testing and no case identification, a finding consistent with previous published results.

O.6.1 Alternative thresholds for case-finding

Since the distribution of total cholesterol is known to vary by age and sex, it is possible that setting the case-finding threshold at the whole study population level value of 9.3 from Futema et al. 2015 would lead to over and under representation in some groups. Alternative data was therefore sought to determine the distribution of total cholesterol in different age/sex groups at the national level. The best available evidence came from the Health

Survey for England (HSE) data, a large sample of the UK general population collected across 7 individual years between 2003 and 2014. All the total cholesterol data in this section were provided by colleagues at the NIHR Diagnostic Evidence Co-operative Newcastle.

Figure 17 Total Cholesterol Distribution by Age and Sex (Curve Fitted)

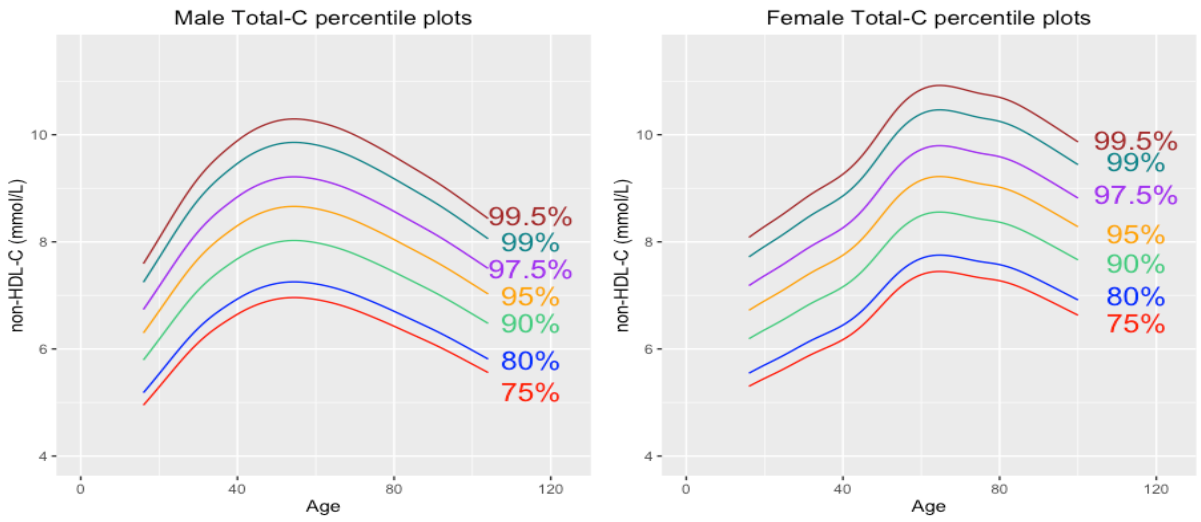


Figure 17 shows the differences in TC distribution by age and sex, with women typically having higher TC under the age of 30, men having higher TC between the ages of 30 and 55 and women having higher TC at age 55+. A blanket whole population TC case-finding threshold may therefore not be appropriate as it would clearly lead to under and over representation from different groups. Based on these distributions, the committee requested the age/sex data shown in Table 73: Total Cholesterol Thresholds by Age/Sex Group (HSE 2003-2013)Table 73 be extracted from the HSE data. The 99.5th percentile data have been highlighted. The percentile equivalent limits of the confidence intervals were calculated via the binomial approximate method. For example, the confidence interval for the 99.5th percentile in the 16-29 'all people' group runs from the value observed at the 99.27th percentile to the value observed at the 99.73rd percentile. Reading from the table, it can be inferred that these values would be slightly higher than 7.36 and slightly lower than 7.95.

Table 73: Total Cholesterol Thresholds by Age/Sex Group (HSE 2003-2013)

	Age Group	97.50%	99%	99.25 %	99.50 %	99.75 %	N	LCL	UCL
All people	16-29	6.70	7.20	7.36	7.60	7.95	3,783	99.27%	99.73%
	>30	8.10	8.60	8.80	9.00	9.30	22,897	99.41%	99.59%
Men	16-29	6.60	7.10	7.40	7.70	8.07	1,737	99.16%	99.84%
	>30	7.90	8.40	8.60	8.80	9.16	9,758	99.36%	99.64%
Women	16-29	6.79	7.20	7.30	7.48	7.88	2,046	99.19%	99.81%
	>30	8.10	8.70	8.90	9.03	9.50	13,139	99.38%	99.62%
All people	16-24	6.40	6.80	6.97	7.11	7.40	2,174	99.20%	99.80%
	25-34	7.10	7.70	8.00	8.20	8.58	3,698	99.27%	99.73%
	>35	8.10	8.60	8.80	9.00	9.40	20,808	99.40%	99.60%
Men	16-24	6.30	6.60	6.62	6.78	6.90	1,040	99.07%	99.93%
	25-34	7.40	8.10	8.22	8.50	8.81	1,568	99.15%	99.85%
	>35	7.90	8.40	8.60	8.80	9.18	8,887	99.35%	99.65%
Women	16-24	6.50	7.00	7.25	7.40	7.62	1,134	99.09%	99.91%

	Age Group	97.50%	99%	99.25 %	99.50 %	99.75 %	N	LCL	UCL
	25-34	6.98	7.30	7.40	7.77	8.17	2,130	99.20%	99.80%
	>35	8.20	8.70	8.90	9.10	9.60	11,921	99.37%	99.63%
All people	<34	7.00	7.40	7.60	8.00	8.43	5,872	99.32%	99.68%
	>55	8.30	8.80	8.90	9.10	9.60	10,162	99.36%	99.64%
	35-54	7.80	8.40	8.50	8.80	9.20	10,646	99.36%	99.64%
Men	<34	7.10	7.69	8.00	8.20	8.55	2,608	99.23%	99.77%
	>55	7.80	8.30	8.40	8.60	8.80	4,326	99.29%	99.71%
	35-54	8.00	8.50	8.80	9.00	9.36	4,561	99.29%	99.71%
Women	<34	6.80	7.30	7.40	7.60	8.07	3,264	99.26%	99.74%
	>55	8.50	9.00	9.10	9.38	10.14	5,836	99.32%	99.68%
	35-54	7.80	8.20	8.40	8.60	9.08	6,085	99.32%	99.68%

Regardless of how the top 0.05% of the population is defined, the absolute number of people affected by the primary care case finding strategies in the economic model would be similar if the prevalence of FH within these subdivided groups does not greatly differ. Given that FH is strongly associated with high TC, this is perhaps a defensible assumption and one the Guideline Committee found plausible although no relevant data more nuanced than that used in the economic model could be found. Sensitivity analysis on the age/sex distribution of those found in the case finding strategies in the model was not undertaken due to lack of suitable data. However, it is obvious from the outputs of the long term treatment model (Table 74) in different age/sex groups that any case finding strategy that increases the proportion of young people among those found will increase the cost-effectiveness of case finding. As noted in O.3.4, treating FH may even be cost saving in younger people and those at the highest risk of CVD events. As shown in the results of the sensitivity analysis (O.4.2), the prevalence of FH would have to be extremely low (~3.5%) before primary care case finding becomes cost-ineffective.

Table 74: Long Term Difference in Costs and QALYs between Treated and Untreated FH

Age	QRISK2	Males Inc. Costs	Males Inc. QALYs	Females Inc. Costs	Females Inc. QALYs
40	30%	-£3,365	1.47	-£2,717	1.32
40	25%	-£3,185	1.57	-£2,721	1.47
40	20%	-£2,750	1.63	-£2,546	1.59
40	15%	-£1,897	1.60	-£2,001	1.65
40	10%	-£375	1.43	-£729	1.55
50	30%	-£3,226	1.32	-£3,021	1.25
50	25%	-£2,801	1.38	-£2,879	1.36
50	20%	-£2,114	1.38	-£2,480	1.42
50	15%	-£1,060	1.31	-£1,659	1.41
50	10%	£506	1.12	-£168	1.26
60	30%	-£1,495	1.09	-£2,351	1.08
60	25%	-£919	1.07	-£1,845	1.11
60	20%	-£176	1.01	-£1,115	1.10
60	15%	£768	0.91	-£96	1.02
60	10%	£1,951	0.75	£1,292	0.87
70	30%	£771	0.68	£254	0.79

Age	QRISK2	Males Inc. Costs	Males Inc. QALYs	Females Inc. Costs	Females Inc. QALYs
70	25%	£1,142	0.64	£658	0.76
70	20%	£1,579	0.60	£1,160	0.70
70	15%	£2,090	0.53	£1,775	0.63
70	10%	£2,684	0.46	£2,521	0.53

O.7 References

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