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Abstract

Elucigene FH20 and LIPOchip for the diagnosis of familial hypercholesterolaemia: a systematic review and economic evaluation

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Background: Familial hypercholesterolemia (FH) is an autosomal dominant genetic condition causing a high risk of coronary heart disease. The prevalence of this disease is about 1 in 500 in the UK, affecting about 120,000 people across the whole of the UK. Current guidelines recommend DNA testing, however, these guidelines are poorly implemented, therefore 102,000 or 85% of this group remain undiagnosed.
Objectives: To assess the diagnostic accuracy, effect on patient outcomes and cost-effectiveness of Elucigene FH20 and LIPOchip for the diagnosis of FH.
Data sources: Electronic databases including MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, BIOSIS, Science Citation Index, Conference Proceedings Citation Index – Science and Cochrane Controlled Trials Register were searched until January 2011.
Review methods: A systematic review of the literature on diagnostic accuracy was carried out according to standard methods. An economic model was constructed to assess the cost-effectiveness of alternative diagnostic strategies for the confirmation of clinically diagnosed FH in index cases and for the identification and subsequent testing of first-, second- and possibly third-degree biological relatives of the index case. Twelve strategies were evaluated linking diagnostic accuracy to treatment outcomes and hence quality-adjusted life-years (QALYs). Deterministic and probabilistic sensitivity analyses were undertaken to investigate model and parameter uncertainty.
Results: Fifteen studies were included for diagnostic accuracy; three reported Elucigene FH20, five reported LIPOchip, four reported low-density lipoprotein cholesterol (LDL-C) tests and three reported an age- and gender-specific LDL-C test against a reference standard of comprehensive genetic analysis (CGA). Sensitivity ranged from 44% to 52% for Elucigene FH20 and from 33.3% to 94.5% for various versions of LIPOchip in detecting FH-causing mutations in patients with a clinical diagnosis of FH. For LIPOchip version 10 (designed to detect 189 UK specific mutations), sensitivity would be 78.5% (based on single-centre data – Progenika, personal communication). For all other Elucigene FH20 or LIPOchip studies (apart from one LIPOchip study), specificity could not be calculated as no false-positive results could be derived from the given data. The LDL-C test was generally

reported to be highly sensitive but with low specificity. For age- and gender-specific LDL-C cut-offs for cascade testing, sensitivity ranged from 68% to 96%. One UK-based study reported sensitivity of 91% and specificity of 93%. For the cost-effectiveness review, only one study reporting cost-effectiveness of any one of the comparators for this assessment was identified. Pre-screen strategies such as Elucigene FH20 followed by CGA were not cost-effective and were dominated by the single more comprehensive tests (e.g. CGA). Of the non-dominated strategies, Elucigene FH20, LIPOchip platform (Spain) and CGA were all cost-effective with associated incremental cost-effectiveness ratios (ICERs) relative to LDL-C of dominance (test is less costly and more effective), £871 and £1030 per QALY gained respectively. CGA generates the greatest QALY gain and, although other tests have lower ICERs relative to LDL-C, this is at the expense of QALY loss compared with the CGA test. Probabilistic sensitivity analysis shows that CGA is associated with an almost 100% probability of cost-effectiveness at the conventional value of willingness to pay of £20,000 per QALY gain.

Limitations: There was much uncertainty regarding the diagnostic accuracy of the included tests, with wide variation in sensitivity across reported studies. A lack of published information for the most recent version of LIPOchip created additional uncertainty, especially in relation to the chip's ability to detect copy number changes. For the economic modelling, we aimed to choose the best studies for the base-case sensitivity of the tests; however, a number of informed choices based on clinical expert opinion had to be made in the absence of published studies for a number of other parameters in the modelling. This adds some uncertainty to our results, although it is unlikely that these would be sufficient in magnitude to alter our main results and conclusions.

Conclusions: As targeted tests designed to detect a limited number of genetic mutations, Elucigene FH20 and LIPOchip cannot detect all cases of FH, in contrast with CGA. CGA is therefore the most effective test in terms of sensitivity and QALY gain, and is also highly cost-effective with an associated ICER of £1030 per QALY gain relative to current practice (LDL-C). Other tests such as Elucigene FH20 and LIPOchip are also cost-effective; however, because of inferior sensitivity compared with CGA, these tests offer cost savings but at the expense of large QALY losses compared with CGA. Further prospective multicentred studies are required to evaluate the diagnostic accuracy of new and emerging tests for FH with the LDL-C test in patients with a clinical diagnosis based on the Simon Broome criteria. Such studies should verify both test-positive and -negative results against a reference standard of CGA and should include a full economic evaluation.

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Contents

Glossary

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader.

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. Therefore, one copy of the mutant gene is sufficient to express the phenotype. Individuals with autosomal dominant diseases have a 50 : 50 chance of passing the mutant gene, and therefore the disorder, on to each of their children.

Cascade testing A mechanism for identifying people at risk of a genetic condition by a process of family tracing. Relatives of the individual diagnosed with familial hypercholesterolaemia are tested for the condition, as are their relatives; ideally, cascade testing should be undertaken in first-, second- and third-degree relatives. For familial hypercholesterolaemia the test employed is measurement of (low-density lipoprotein) cholesterol in the blood and/or a DNA test if a disease-causing mutation has been identified in the proband/index.

Coronary heart disease An abnormal condition characterised by narrowing of the small blood vessels that supply blood and oxygen to the heart (coronary heart disease is synonymous with coronary artery disease).

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

Heterozygous familial hypercholesterolaemia High low-density lipoprotein cholesterol concentration in the blood caused by an inherited mutation from one parent only.

Homozygous familial hypercholesterolaemia Very high low-density lipoprotein cholesterol level in the blood caused by an inherited mutation from both parents. When a person inherits exactly the same affected gene from both parents this is called truly 'homozygous' familial hypercholesterolaemia. When the mutations in the low-density lipoprotein receptor gene (or equivalent) are different, this state is called 'compound heterozygous'.

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

***p*-value** The probability that an observed difference could have occurred by chance if the null hypothesis is true. A p-value of < 0.05 is conventionally considered to be statistically significant.

Proband The affected (index) individual through whom a family with a genetic disorder is ascertained. The terms 'index case', 'index individual', 'index patient' and 'proband' are synonymous with one another in this report.

Second-degree relatives A person's biological grandparent, uncle, aunt, niece, nephew, half-sister or half-brother.

Tendon xanthoma/xanthomata 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 familial hypercholesterolaemia that most frequently affects the Achilles tendons but can also involve tendons on the back of the hands, elbows and knees.

Third-degree relatives A person's biological great-grandparent, great-grandchild, great-aunt, great-uncle, first cousin, grand-nephew or grand-niece.

List of abbreviations

APOB	apolipoprotein B
ARMS	amplification refractory mutation system
BNF	*British National Formulary*
CEAC	cost-effectiveness acceptability curve
CG71	clinical guideline number 71
CGA	comprehensive genetic analysis
CHD	coronary heart disease
CI	confidence interval
CMGS	Clinical Molecular Genetics Society
DFH	definite familial hypercholesterolaemia
DGGE	denaturing gradient gel electrophoresis
dHPLC	denaturing high-performance liquid chromatography
Ext Dom	Extendedly dominated
FH	familial hypercholesterolaemia
ICER	incremental cost-effectiveness ratio
iPLEX	multiple MassARRAY spectrometry
LDL-C	low-density lipoprotein cholesterol
LDLR	low-density lipoprotein receptor
MedPed	make early diagnosis, prevent early death
MI	myocardial infarction
MLPA	multiplex ligation-dependent probe amplification
MOLU	MOLecular Unit
N/A	not applicable
NA	not available
NC	not calculable
NICE	National Institute for Health and Clinical Excellence
NR	not reported
PAD	peripheral arterial disease
PBR	Payment by Results
PCR	polymerase chain reaction
PCSK	protein convertase subtilisin/kexin
PCVD	premature cardiovascular disease
PFH	possible familial hypercholesterolaemia
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life-year
QMFSP	quantitative multiplex PCR methodology
RCT	randomised controlled trial
SROC	summary receiver operating characteristic
SSCP	single-strand conformation polymorphism
TC	total cholesterol
UFH	unclassified familial hypercholesterolaemia
UKGTN	United Kingdom Genetic Testing Network

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Background

Familial hypercholesterolaemia (FH) is an autosomal dominant genetic condition causing a risk of premature coronary heart disease (CHD). In the UK, prevalence is estimated at 1 in 500, affecting around 100,000 people in England, around 6000 in Wales and approximately 10,000 in Scotland. At least 85% (around 102,000) of people with FH in the UK remain undiagnosed. Current guidelines recommend DNA testing using comprehensive genetic analysis (CGA) by mutation screening of the low-density lipoprotein receptor (*LDLR*) gene, using sequencing and dosage analysis by multiplex ligation-dependent probe amplification (MLPA), and targeted testing for specific mutations in apolipoprotein B (*APOB*) and protein convertase subtilisin/kexin (*PCSK9*). It has been suggested that use of assay systems targeted to detect the most common FH mutations in a population might either replace CGA or be usefully used as a pre-screen to reduce the number of samples requiring the apparently more expensive CGA. Elucigene™ FH20 (Gen-Probe Life Sciences, UK) and LIPOchip® (Progenika Biopharma, Spain) are commercially available genetic tests designed to detect mutations that are most frequent in a European Caucasian population.

Objectives

The aim of this assessment is to assess the diagnostic accuracy, effect on patient outcomes and cost-effectiveness of Elucigene FH20 and LIPOchip for the diagnosis of FH.

Methods

Studies were identified by searching electronic databases and relevant websites, contact with experts in the field and the scrutiny of bibliographies of retrieved papers. The date of the last search was January 2011. Types of studies considered were randomised controlled trials, direct comparative diagnostic studies, diagnostic cross-sectional studies and case–control studies. The populations considered were adults and children with a clinical diagnosis of FH (index cases) based on the Simon Broome, Dutch or MedPed (make early diagnosis, prevent early death) criteria and, for cascade testing, the first-, second- and third-degree biological relatives of the index cases. The intervention (index) tests considered were Elucigene FH20 and LIPOchip and the comparators considered were low-density lipoprotein cholesterol (LDL-C) concentration measurement as part of the Simon Broome, Dutch or MedPed criteria in the diagnosis of index cases and, for relatives, targeted gene sequencing (the genetic test for sequencing a specific part of the gene where the family mutation is found) and gender- and age-specific LDL-C criteria as recommended in the National Institute for Health and Clinical Excellence (NICE) clinical guideline CG71. The reference standard considered was CGA in combination with Simon Broome, Dutch or MedPed criteria. These criteria primarily include a combination of high cholesterol, presence of tendon xanthomata in the patient or first-degree relative or a family history of premature CHD or high cholesterol.

Two reviewers screened the titles, abstracts and full-text papers of all articles identified by the search strategy. Data extracted by one reviewer were checked by a second reviewer. Two reviewers independently assessed the quality of the diagnostic studies using a modified

version of the QUADAS instrument. For each study, where there was sufficient information, sensitivity, specificity and positive and negative likelihood ratios and their confidence intervals were calculated. Because of the heterogeneous nature of the studies, no formal meta-analysis was undertaken although sensitivity results were presented graphically as forest plots without pooled estimates.

An economic model was constructed in Microsoft Excel™ to assess the cost-effectiveness of alternative diagnostic strategies for the confirmation of clinically diagnosed FH in index cases and for the identification and subsequent testing of first-, second- and possibly third-degree biological relatives of the index case. The model described care pathways from clinical diagnosis through treatment over a lifetime horizon using predominantly statin-based therapies. The main tests considered were LDL-C (current practice), CGA (recommended indirectly by NICE CG71), Elucigene FH20 and LIPOchip. Test strategies in which MLPA was used as an add-on test to either Elucigene FH20 or LIPOchip were also considered. These tests were combined into a total of 12 different diagnostic testing strategies, all of which represented potential testing strategies in clinical practice. The main analysis refers to the comparison of each strategy with current practice (LDL-C); however, a comparison against CGA is also considered. The main analysis also refers to the combined process of confirming a clinical diagnosis in index cases and cascade testing of relatives; however, additional analysis also considered the identification of index cases only. Data from the diagnostic accuracy review were used in the development of the model. Costs associated with each diagnostic test were based on the MOLecular Units (MOLU) system, which assigns genetic tests to predetermined bands based on the test complexity. Total MOLUs were calculated and multiplied by a cost of £30 per MOLU to cost each strategy. Additional costs associated with cardiovascular events, treatments and NHS staff time were sourced from standard NHS reference cost sources (Payment by Results, *British National Formulary* and Personal Social Services Research Unit). Quality-adjusted life-years (QALYs) were estimated based on treatment effect and reduced cardiovascular events and therefore a cost–utility analysis was carried out, with incremental cost-effectiveness ratios (ICERs) presented for the base case and a range of deterministic sensitivity analyses undertaken to assess uncertainties in the estimates and assumptions. Probabilistic sensitivity analysis was also carried out using the net benefit approach with the results presented as cost-effectiveness acceptability curves.

Results

Diagnostic performance

Fifteen studies (seventeen articles) reported the performance of Elucigene FH20 (three studies), LIPOchip (five studies), LDL-C tests (four studies) and age- and gender-specific LDL-C (three studies) against a reference standard of CGA in which participants received a clinical diagnosis of FH using the Simon Broome, MedPed or Dutch criteria. Three of these studies reported targeted gene sequencing. Only studies published as full-text articles were quality assessed (one reporting Elucigene FH20, two reporting LIPOchip and six reporting LDL-C). The included studies on Elucigene FH20 and LIPOchip reported a sequential genotyping test in which (1) the participants received a clinical diagnosis of FH followed by the index test (as a pre-screen) and then (2) those who tested negative received further genetic investigations such as gene sequencing and MLPA. Overall, the participants were representative of those who would receive the test in practice (all received a clinical diagnosis of FH using Simon Broome, Dutch or MedPed criteria). The Elucigene FH20 and LIPOchip studies suffered from partial and differential verification bias (not all patients received a reference standard test and patients did not receive the same reference standard test regardless of the index test result respectively), whereas all but one of the LDL-C studies avoided these biases. Only one study reporting Elucigene FH20, one reporting LIPOchip and three (50%) of the LDL-C studies used CGA as defined in the assessment.

Sensitivity ranged from 44% to 52% for Elucigene FH20 and was 78.5% for LIPOchip version 10 (designed to detect 189 UK-specific mutations, based on data received from the manufacturer) in detecting FH-causing mutations in patients with a clinical diagnosis of FH based on the Simon Broome criteria. The LIPOchip designed to detect 251 mutations that were not specific to the UK showed 33.3–56.9% sensitivity. Specificity of 93.8% (one false-positive) was reported for LIPOchip version 8 against CGA. The Elucigene FH20 kit had higher sensitivity in those with a clinical diagnosis of definite FH (49%) than in those with a clinical diagnosis of possible FH (40%).

The LDL-C test was generally reported to be highly sensitive against a reference standard of CGA. In two studies, the LDL-C test as part of the Simon Broome criteria had high sensitivity (90% and 93%) but low specificity (28% and 29%) in detecting FH. One study reported higher sensitivity of LDL-C cut-offs as part of the MedPed criteria in children (81%) than in adults (66%). For age- and gender-specific LDL-C cut-offs for cascade testing, sensitivity ranged from 68% to 96%. One study reported sensitivity of 91% and specificity of 93% for cascade testing in a cohort from the UK. Sensitivities of 68%, 79%, and 84% and specificities of 85%, 85% and 84% in cohorts of first-degree relatives from the Netherlands, Denmark and Norway, respectively, were reported.

Cost-effectiveness

We identified one study that evaluated LIPOchip as a cascade testing strategy for identification of index cases and the testing of first-degree relatives of the index case. The comparator for the assessment was no cascade testing. The ICER was estimated as €3243 per life-year gained and there was a 94% probability of cost-effectiveness at a willingness to pay of €7400 per life-year gained. We did not identify any additional studies or models evaluating the candidate tests.

In relation to confirming the clinical diagnosis and identifying patients for cascade testing, single test strategies such as CGA dominate combination test strategies of CGA testing for those who initially test-negative on Elucigene FH20 or LIPOchip [e.g. CGA is less costly and generates greater QALY gain than Elucigene FH20/LIPOchip followed by CGA for negatives (on the initial test)]. The base-case analysis shows that, for a cohort of 1000 index cases tested, CGA is £4.6M more costly but also generates an additional 4487 QALYs compared with current practice (LDL-C). The associated ICER is £1030 per QALY gained. In addition to the cost-effectiveness of CGA, a number of other strategies may be potentially considered cost-effective with ICERs falling below that reported for CGA. Elucigene FH20 as a stand-alone testing strategy is less costly, more effective and thus dominant compared with LDL-C. LIPOchip platform (Spain) had an ICER of £871 per QALY gained. The difficulty, however, is that the cost-effectiveness of these tests is driven by cost savings relative to CGA, but also QALY losses. In fact, compared with CGA, all other testing strategies generate inferior sensitivity to CGA and are thus associated with fewer QALY gains. The sequences of the presented ICERs do not change for age subgroup analysis or for a range of plausible deterministic sensitivity analyses undertaken. Probabilistic sensitivity analysis suggests that, for willingness to pay for QALY gain values $\geq$ £3500, there is a $>$ 90% probability of CGA being the most cost-effective strategy relative to LDL-C. Some slight variation is evident depending on age subgroup and prevalence for low ceiling ratios of willingness to pay for a QALY gain; however, the message that CGA is the most likely cost-effective strategy remains for all ceiling ratios $>$ £5000 regardless of age or prevalence rate. The probability of CGA being the most cost-effective testing strategy increases to almost 100% at the conventional value of willingness to pay of £20,000 per QALY gained.

Discussion

The results reported here are based on a small number of studies. There was no published evidence on LIPOchip version 10; data for LIPOchip version 10 were available from the

manufacturer. The evidence on LIPOchip version 10 and Elucigene FH20 suggests that approximately 20–50% of FH-causing mutations will be missed using these targeted tests alone among those who have a clinical diagnosis of FH based on Simon Broome criteria. Further genetic testing with sequencing and MLPA would potentially detect the FH cases missed by Elucigene FH20 or LIPOchip. The LDL-C tests compared with a reference standard of CGA were generally observed to be highly sensitive in both index cases and cascade testing of relatives. However, two of the LDL-C studies used CGA that did not include the analysis of the *APOB* and *PCSK9* genes, which would not necessarily detect all cases of FH, and in addition there may be other genes as yet unrecognised that may give rise to the FH phenotype. It was not possible to calculate specificity for Elucigene FH20 and LIPOchip version 10 as none of the test-positives went on to receive CGA; therefore, it was not known whether or not there were any false-positive results. One false-positive diagnosis with LIPOchip version 8 (does not contain five mutations that are present in the Elucigene FH20 kit) was reported in a study with a small sample size ($n = 22$). LDL-C test performance in both index cases and cascade testing of relatives (except for LDL-C as a part of MedPed criteria) reported lower specificity with a high number of false-positive diagnoses in terms of people with a clinical diagnosis of FH having no FH-causing mutation detected.

Comprehensive genetic analysis is the most sensitive test and hence generates the greatest QALY gain of all tests and is therefore highly cost-effective. Other less sensitive non-dominated tests such as Elucigene FH20 and LIPOchip (Spain) are slightly more cost-effective but generate lower QALY gains than CGA. In addition, CGA detects all known FH-causing mutations, thereby eliminating any ethical or equity issues involved with the process. Additionally, it was not possible to link the utility of diagnostic information to treatment outcome and QALY gains; however, it is highly unlikely that this would be meaningful in the context of the quality of life gained from lifelong treatment for FH. The economic modelling was associated with a number of assumptions that add uncertainty to the results. First, there is much variation in test sensitivity, especially surrounding the LIPOchip estimates. Assumptions have also been made around the number of relatives who do not have a mutation but who may have high cholesterol. A further limitation of the analysis refers to the accuracy of test sensitivity and specificity differentials between those relatives of genetically negative index cases and those relatives of genetically confirmed index cases. Finally, there is much uncertainty among clinicians in how best to treat FH and non-FH patients with high cholesterol. Many may start with a low-intensity treatment and increase treatment intensity if a satisfactory response is not achieved. Others believe that, as statin therapy generates very few adverse events, it would be appropriate to treat everyone with a high-intensity statin (e.g. atorvastatin). We have tested all assumptions made in deterministic and probabilistic sensitivity analysis and find that the model outcomes are robust to assumptions surrounding treatment choice. Although some variations exist in the ICERs reported, all remain < £20,000 per QALY gained and the results of the probabilistic sensitivity analysis broadly confirm the deterministic analyses.

Generalisability of the findings

The frequency of FH-causing mutations can vary by country of origin and within countries by ethnicity. As Elucigene FH20 and LIPOchip kits are designed to detect a limited number of mutations, the sensitivities of both of the kits are largely dependent upon the prevalence of these specific FH-causing mutations in the population. Therefore, the sensitivities observed here may not be generalisable to other populations or ethnic groups. Even within the UK, some variation in the detection rate of FH-causing mutations by Elucigene FH20 across six centres was observed. Given this variation in the prevalence of FH-causing mutations that are detectable by Elucigene FH20 and LIPOchip, CGA gives the most accurate test results available and would appear to be generalisable to the whole of the UK population.

Conclusions

Implications for service provision

Based on evidence that was limited in quantity and of variable quality, Elucigene FH20 and LIPOchip version 10 (designed to detect 189 UK-specific mutations) have been shown to detect 44–52% and 78.5%, respectively, of FH-causing mutations that are also detected by CGA amongst people with a clinical diagnosis of FH based on the Simon Broome criteria. As targeted tests designed to detect a limited number of genetic mutations, Elucigene FH20 and LIPOchip cannot detect all cases of FH; therefore, further genetic screening using MLPA and sequencing is still required to give an unequivocal diagnosis of FH. Using the LDL-C test (high sensitivity and low specificity) as part of the Simon Broome criteria means that a large number of people will receive a clinical diagnosis of FH who will not have a detectable FH-causing mutation.

Comprehensive genetic analysis appears to provide a favourable cost-effective method of diagnosis, with an associated ICER of £1030 per QALY gain. Elucigene FH20 and LIPOchip (Spain) are even more cost-effective in terms of deterministic analysis because of their lower costs; however, they generate substantially lower QALYs than CGA (which is also highly cost-effective). Cost-effectiveness (for Elucigene FH20 in particular) is driven primarily by the cost savings associated with the test. There may be practical and resource issues associated with full-scale implementation in the recommending of CGA for everyone with a clinical diagnosis of FH. If so, then a judgement is required whether or not it is ethical to implement cascade testing based on an index test result that is less sensitive than CGA (e.g. Elucigene FH20/LIPOchip). Doing so would mean that potentially FH-positive relatives will be missed. These patients may not get potentially life-saving treatment if index patients are managed only on the basis of their clinical diagnosis as opposed to their genetic test.

As there are an estimated 100,000 undiagnosed people with FH in the UK, the testing and treatment of all will place a substantial resource burden on already tight NHS budgets. On the other hand, costs associated with genetic testing are reducing and will continue to do so with the emergence of next-generation sequencing techniques. 'Next generation' refers to the emergence in recent years of new (non-Sanger-based) DNA sequencing techniques. This allows higher throughput in genetics laboratories to test for more mutations, more quickly, and hence reduce costs. Early estimates suggest that the emergence of next-generation sequencing may reduce the sequencing costs in the testing of FH by approximately 40%. Costs of treatment are also likely to reduce in the near future as atorvastatin is due to come off patent in 2011 with an expected retail cost similar to that of generic simvastatin.

Suggested research priorities

- A prospective multicentre study comparing the performance of Elucigene FH20 and LIPOchip with the LDL-C test in patients with a clinical diagnosis of FH based on the Simon Broome criteria, in which both test-positives and test-negatives are verified against a reference standard of CGA, would be informative. Such a study should also include subgroup analysis of the performance of the tests in different ethnic groups, if possible have a period of follow-up to allow provision of relevant longer-term clinical effectiveness outcomes and incorporate an economic evaluation. An economic evaluation should consider the effect of utility of diagnostic information (false-negative results or false-positive results) on survival and quality of life in FH patients. Such information could be used to inform the estimation of QALYs in future modelling exercises.
- There is little evidence linking efficacy of statins in children to the onset of CHD. There is a need to assess the relative risks of onset of disease in this group of patients.

- There is a need for a systematic review of all of the FH-causing mutations currently detectable in the UK population as a whole and in specific ethnic groups and their associated impact on risk of CHD.
- There is a need for ongoing clinical research to continue to update the list of genes and mutations which are linked to FH. As a result, the positive detection rate for CGA (i.e. mutation prevalence) needs to be updated to reflect such new discoveries on a regular basis.
- It was outwith the scope of this review to assess tests such as multiple MassARRAY spectrometry (iPLEX) that may also be used for detecting FH but are not as yet CE marked for this purpose. Therefore, further research into the diagnostic accuracy and cost-effectiveness of this test would be informative.

Funding

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Chapter 1

Background and definition of the decision problem

Description of health problem

Introduction

Familial hypercholesterolaemia (FH) is a genetic condition in which people inherit an abnormal (mutant) gene that affects the rate at which cholesterol is cleared from the blood, giving rise to a high level of cholesterol in the bloodstream. An individual can inherit a mutant gene either from one parent (a condition known as heterozygous FH) or from both parents (a condition termed as homozygous FH or compound heterozygous FH). Homozygous FH occurs if a person inherits two copies of exactly the same gene alteration from each parent. Compound heterozygous FH occurs when a person inherits two different types of gene alterations, one from each parent. A person with homozygous FH or compound heterozygous FH usually has a much more severe form of the disease than someone with heterozygous FH. Almost all people with FH have heterozygous FH.

Affected individuals have raised cholesterol concentrations from birth, and this leads to early development of atherosclerosis and coronary heart disease (CHD), and high risk of premature death. FH is generally characterised by the presence of physical symptoms such as tendon xanthomata (cholesterol deposits) and arcus cornealis (cholesterol deposits in eyes) and clinical symptoms (high cholesterol levels).

However, treatment from late childhood with statin therapy, combined with lifestyle changes such as stopping smoking, healthy eating and exercising, can restore normal life expectancy. A recent National Institute for Health and Clinical Excellence (NICE) guideline on the identification and management of FH reviewed strategies for case ascertainment and effective treatment.[1] A key element was the recommendation that cascade testing of first-, second- and if possible third-degree relatives of affected individuals should be offered. Such cascade testing should be carried out either by offering DNA-based testing to consenting individuals or by biochemical measurement of cholesterol levels.[1]

Aetiology, pathology and prognosis

The major aetiological determinant of FH is the presence of a highly penetrant mutation (penetrance refers to the proportion of individuals with the mutation who exhibit clinical symptoms) in a gene important in cholesterol metabolism. FH is mainly caused by a mutation in the low-density lipoprotein receptor (*LDLR*) gene, which is found on the short form of chromosome 19 and is responsible for primary hepatic low-density lipoprotein cholesterol (LDL-C) uptake, processing up to 70% of circulating LDL-C. LDL-C is bound to the receptor (a structural protein molecule on the cell surface that binds to a specific factor, such as a drug or other molecules) and then transported into the cell, where it is metabolised. High-affinity LDLRs are found in the endothelium, smooth muscle cells and liver. In FH, there are four groups of mutations leading to a high level of total cholesterol (TC) and LDL-C:

- those resulting in impaired receptor synthesis

- those resulting in impaired transport of receptors to the cell surface
- those resulting in failure of LDL-C to bind the LDLR properly
- those resulting in failure to transport bound LDL-C into the cell.

Mutations associated with FH have also been found in the apolipoprotein B (*APOB*) and protein convertase subtilisin/kexin 9 (*PCSK9*) genes but with fewer variants than in the *LDLR* gene. The *APOB* gene makes a protein that helps hold cholesterol-carrying lipoproteins together in the blood. If there is an alteration in this gene, the LDL does not bind well to the LDLRs on the surface of the liver and it is removed only slowly from the blood. If there is an alteration to the *PCSK9* gene, more LDLRs are broken down in the liver, resulting in fewer to remove LDL from the blood. The result in both cases is that the level of LDL-C in the blood remains high. The overall effect of these gene alterations is that the liver is less able to take up excess cholesterol from the blood, meaning that less is excreted into the intestines, from where it can be removed from the body.[2]

As the gene is inherited in an autosomal dominant manner, the probability of inheriting the condition is 50% in first-degree biological relatives (parents, siblings, children), 25% in second-degree relatives (aunts, uncles, grandparents, nieces, nephews) and 12.5% in third-degree relatives (first cousins and siblings of grandparents).[3]

High cholesterol levels in the blood have complex causes, with genetic and environmental causes operating simultaneously[4]. As with all genetic conditions, there are several other genes and metabolic and environmental factors contributing to the clinical course of the condition:[4]

- examples of genetic causes: specific mutations leading to the FH phenotype, genetic factors that influence lipoprotein metabolism, genetic factors that influence CHD
- examples of metabolic causes: hormonal, diet/body weight, lipoproteins and enzymes and apolipoproteins modulating their metabolism, factors involved in inflammation, clotting and thrombosis
- examples of environmental causes: prevalence of CHD in the community, drugs affecting lipoprotein metabolism used without identifying FH.

There is strong evidence that smoking greatly increases the risk of CHD in FH and modest evidence that diet is an important contributory factor.

Familial hypercholesterolaemia is latent (presymptomatic period) from birth to the second decade of life and if diagnosed by then can be successfully treated. FH is usually evident (by blood cholesterol levels) in the first year of life and physical signs such as xanthomata are seen in the second decade of life. Tendon xanthomata are frequent but not always present. Symptomatic CHD usually appears by the fourth decade of life. People with heterozygous FH usually have LDL-C levels that are double the normal level (with TC often between 7.5 and 10 mmol/l), and receptor activity that is about half the normal level.[5] People with homozygous FH typically present with very severe hypercholesterolaemia, with LDL-C levels six times the normal level (i.e. LDL-C levels 15–20 mmol/l) and early onset of disease in childhood.[5]

If untreated, approximately 50% of men and 30% of women with FH will develop CHD by age 60 years[6] and around 50% of men will die before the age of 60 years.[7] People with homozygous FH have a significantly poorer prognosis than those with heterozygous FH and most will die before the age of 30 years. However, the risk of CHD can be greatly reduced if FH is diagnosed before the onset of the condition, by treatment with lipid-modifying drug therapy (statins) in combination with lifestyle changes.[1] Statins have been shown to be effective in lowering the risk of mortality from CHD in patients with clinical FH (see *Figures 1* and *2*).[8,9]

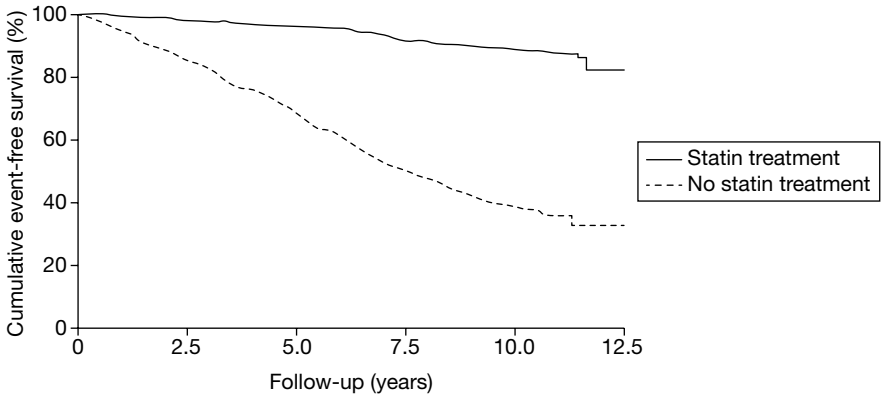

FIGURE 1 Kaplan–Meier curve showing the cumulative event-free survival in patients with and without statin treatment. Source: Versmissen *et al*.[8]

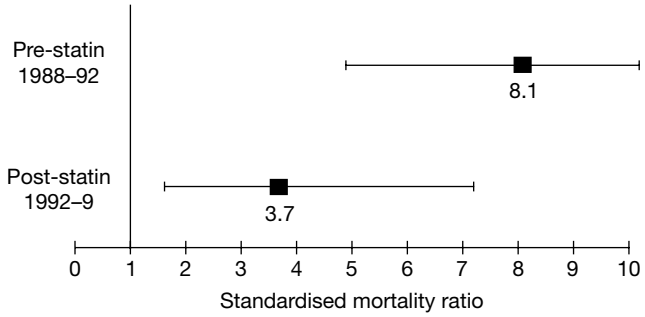

FIGURE 2 Pre- and post-statin death rates in FH patients (20–59 years). Source: Department of Health Familial Hypercholesterolemia Cascade Testing Audit Project.[10]

Epidemiology, incidence and prevalence

It has been estimated that worldwide around 10 million people have FH, of whom around 200,000 die each year from CHD.[11] The prevalence of heterozygous FH varies in different populations. In the UK, prevalence is estimated at 1 in 500, affecting around 100,000 people in England, around 6000 in Wales and approximately 10,000 in Scotland. Homozygous FH and compound heterozygous FH are much rarer, with a prevalence of 1 in 1 million.[12] The frequency of FH-causing mutations can vary by country and within countries by ethnicity. The Centre for Cardiovascular Genetics (University College London)[13] keeps an up-to-date database of genetic mutations associated with FH.

The *LDLR*, *APOB* and *PCSK9* genes are most frequently implicated, but other genes remain to be discovered. Therefore, it is possible that in some people other, yet undiscovered, mutations will not be detected using current genetic strategies. Approximately 1400 unique mutations have been identified worldwide so far, of which over 200 have been reported in the UK population.[14] Approximately 93% of genetic mutations associated with FH occur in the *LDLR* gene, whereas mutations in the *APOB* and *PCSK9* genes account for approximately 5% and 2% of cases respectively.[15]

Impact of the health problem

People with FH have consistently been shown to be at high risk of cardiovascular-associated morbidity and mortality.[9,16] Adults with FH aged 20–39 years have a 100-fold increased risk of dying from CHD.[17] FH is an underdiagnosed condition. It has been estimated that > 85% (around 102,000) of the 120,000 people in the UK thought to be affected with FH are undiagnosed,[18]

putting them at increased risk of CHD. Often a diagnosis is made too late for an individual to benefit from treatment.[1] A definitive diagnosis through DNA screening of suspected FH patients and then testing of their relatives has been identified as the best possible approach to improve diagnosis of FH.[19]

Measurement of disease

Clinical diagnosis

Different sets of clinical criteria have been developed for the diagnosis of FH. These criteria primarily include a combination of high cholesterol, presence of tendon xanthomata in the patient or first-degree relative and a family history of premature CHD or high cholesterol.

The most widely utilised and validated sets of clinical criteria are:

1. the UK Simon Broome Register criteria
2. the US MedPed (make early diagnosis, prevent early death) criteria
3. the Dutch Lipid Clinic Screening Network criteria.

Simon Broome criteria

The Simon Broome criteria include a combination of family history of CHD, physical signs such as tendon xanthomata, cholesterol concentration and DNA testing for the diagnosis of FH (*Table 1*).[5,20] This approach categorises FH as 'definite' or 'possible'. The major distinction between definite and possible FH is the presence of tendon xanthomata in the definite FH cases. DNA-based evidence was subsequently introduced into the criteria for provision of an unequivocal diagnosis of FH. However, around 10% of people with FH do not meet the Simon Broome criteria.

The Simon Broome Register was set up, utilising an endowment donated by his wife Katherine, after his premature death from cardiovascular disease, when he was found to have FH.[21]

MedPed criteria

The US MedPed criteria take account of the prior probability of a *LDLR* mutation, which is different for first-, second- and third-degree relatives and the general population. For each of these groups and for four age groups, different cholesterol level cut off points were then designated (*Table 2*).[5] FH is diagnosed if TC levels exceed the cut off point.

Dutch Lipid Clinic Screening Network criteria

The Dutch criteria[5] are similar to the Simon Broome criteria except that a scoring system is used to distinguish between definite, possible or probable FH (*Table 3*). A diagnosis of FH is definite if the score is > 8 points, probable if the score is 6–8 points and possible if the score is 3–5 points. A score of < 3 points is considered non-FH. The only difference between the Dutch criteria and the Simon Broome criteria is the requirement of tendon xanthomata in the Simon Broome criteria for a diagnosis of definite FH (if a mutation has not been identified).

However, identification of patients by elevated cholesterol levels is not fully reliable. An overlap in blood cholesterol levels between people with FH and those with non-genetic polygenic hypercholesterolaemia has been reported.[22,23] In some FH cases, LDL-C levels are not elevated, resulting in a false-negative diagnosis.[20,24]

Genetic diagnosis

DNA-based mutation screening methods provide a definitive diagnosis of FH by identifying a causative mutation and confirming the clinical diagnosis.[25] DNA testing adds clinical certainty to a diagnosis among relatives. Mutations associated with FH have been mostly found in the

TABLE 1 Simon Broome diagnostic criteria[5,20]

Criteria required for clinical diagnosis of FH	Definite FH	Possible FH
Cholesterol concentration Child/young person: TC > 6.7 mmol/l, LDL-C > 4 mmol/l; adult: TC > 7.5 mmol/l, LDL-C > 4.9 mmol/l	Yes	Yes
Clinical symptoms Tendon xanthomata or evidence of these signs in first- or second-degree relative	Yes	No
Family history of MI in second-degree relative aged < 50 years or in first-degree relative aged < 60 years or Raised TC (> 7.5 mmol/l in adult first- or second-degree relative or > 6.7 mmol/l in child or sibling < 16 years)	No	Yes (at least one of these criteria)

MI, myocardial infarction
Or *DNA-based evidence of mutation* in *LDLR*, *APOB* or *PCSK9* gene gives an unequivocal diagnosis of FH.

TABLE 2 MedPed diagnostic criteria[5]

	LDL-C (mmol/l)			
Age (years)	First-degree relatives with FH	Second-degree relatives with FH	Third-degree relatives with FH)	General population
< 18	5.7	5.9	6.2	7.0
20	6.2	6.5	6.7	7.5
30	7.0	7.2	7.5	8.8
40	7.5	7.8	8.0	9.3

TABLE 3 Dutch Lipid Clinic Screening Network criteria[5]

Criteria	Point
Family history	
First-degree relative with known premature (< 55 years men, < 60 years women) coronary and vascular disease or	1
First-degree relative with known LDL-C > 95th percentile and/or	
First-degree relative with tendon xanthomata and/or arcus cornealis or	
Children < 18 years with LDL-C > 95th percentile	2
Clinical history	
Patient has premature (< 55 years men, <60 years women) coronary artery disease	2
Patient has premature (< 55 years men, <60 years women) cerebral or peripheral vascular disease	1
Physical examination	
Tendon xanthomata	6
Arcus cornealis < 45 years	4
Cholesterol (mmol/l)	
LDL-C ≥ 8.5	8
LDL-C ≥ 6.5–8.4	5
LDL-C ≥ 5.0–6.4	3
LDL-C ≥ 4.0–4.9	1
DNA analysis	
Functional mutation in the *LDLR* present	8

LDLR gene and rarely in the *APOB* and *PCSK9* genes.[26] The *LDLR* gene is divided into 18 exons (coding regions in a gene) and 17 introns (non-coding regions in a gene).[27] There are different types of mutations. Large rearrangements or deletions in the *LDLR* gene have been reported in 5% of FH patients in the UK.[5] Different genetic screening systems are used to screen the entire coding region for the *LDLR* gene, such as single-strand conformation polymorphism (SSCP) analysis, denaturing gradient gel electrophoresis (DGGE), DNA sequencing and RNA analysis.[27] None of these techniques has been reported to be 100% accurate, with detection rates of 75–85%. Techniques such as Southern blot analysis[27] or multiplex ligation-dependent probe amplification (MLPA) are used to identify larger rearrangements and deletions. MLPA analysis, being a simple and rapid method for detecting large rearrangements, has been recommended to be included in the comprehensive genetic analysis (CGA) testing strategy for FH.[28]

Current service provision

Diagnosis and management

The NICE clinical guideline[1] on the identification and management of FH recommends that diagnosis should be based upon the Simon Broome criteria. Health-care professionals should inform people with a diagnosis of FH based on the Simon Broome criteria that they have a clinical diagnosis of FH. To confirm a diagnosis of FH, health-care professionals should undertake two measurements of LDL-C concentration because biological and analytical variability occurs.

The NICE guideline[1] recommends that health-care professionals should 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. Health-care professionals should offer all people with FH a referral to a specialist with expertise in FH for confirmation of diagnosis and initiation of cascade testing in relatives.

Cascade testing using a combination of DNA testing and LDL-C concentration measurement is recommended to identify affected relatives of those index cases with a clinical diagnosis of FH. This should include at least the first- and second- and, when possible, third-degree biological relatives. In families in which a mutation has been identified, the mutation and not LDL-C concentration should be used to identify affected relatives. In the absence of a DNA diagnosis, cascade testing using LDL-C concentration measurements should be undertaken to identify people with FH. To diagnose FH in relatives of an index case, age- and gender-specific criteria for LDL-C concentration should be used, as using the Simon Broome LDL-C criteria for index cases would result in underdiagnosis. The age- and gender-specific LDL-C levels are split into three zones: green (relatives unlikely to have FH), red (relatives are likely to have a clinical diagnosis of FH) and grey (uncertain)[1] (see *Appendices 1* and *2*).

For the management of adults, the NICE guideline[1] recommends that a high-intensity statin should be prescribed to achieve a recommended reduction in LDL-C concentration of > 50% from baseline. Health-care professionals should offer all children and young people diagnosed with, or being investigated for, FH a referral to a specialist with expertise in FH in children and young people. This should be in an appropriate child/young person-focused setting that meets the standards within the *National Service Framework for Children, Young People and Maternity Services*.[29]

Current service cost

Currently, the majority of cascade testing is conducted using LDL-C. This is relatively inexpensive compared with DNA testing; however, it is associated with test inaccuracies. Costs are estimated

to occur over a 5- to 10-year period, after which time the number of cascade tests would be expected to fall. The estimated cost implications for implementing the current NICE guidance in the NHS are shown in *Table 4*.

Cost implications associated with cascade testing will probably be most relevant to secondary care. Savings from reductions in coronary events are likely to apply to both primary and secondary care. It is estimated that the cascade testing process will take approximately 5–10 years. Therefore, costs in year 3 would be expected to be extrapolated in a similar pattern out to 10 years, after which overall cost implications would start to fall as fewer people would require testing and savings from coronary events avoided would continue to increase. The costing report referenced in *Table 4* did not extrapolate over a 10-year time horizon and these numbers are based on strong assumptions about how these costs might change over time. For example, treatment costs are likely to be less than shown owing to the reduction in prices associated with next-generation gene sequencing and the forthcoming reduction in the cost of atorvastatin as it comes off patent. 'Next generation' refers to the emergence in recent years of new (non-Sanger-based) DNA sequencing techniques. This allows higher throughput in genetics laboratories to test for more mutations, more quickly, and hence reduce costs. Early estimates suggest that the emergence of next-generation sequencing may reduce the sequencing costs in the testing of FH by approximately 40%. Therefore, the results presented are a guideline only and should be interpreted with caution. They are not an estimate of the resource use implications from implementing the recommendations of this report. Further details of how the above were derived are available from the NICE website.[1]

Variation in services and/or uncertainty about best practice

A 2004 census of clinics providing specialist lipid services in the UK[30] reported that, of the 165 clinics on Heart UK's database, 144 provided specialist lipid services; however, the service provision was reported to be patchy, with < 10% of the estimated FH patients in the UK recorded on the computerised system. In such a scenario, the implementation of fully effective national cascade testing would be impeded.[30] Furthermore, it was reported that 64% of these clinics employed only one doctor and > 20% did not employ a nurse, with only 22% providing two or more sessions per week (see also *Current usage in the NHS*).

Relevant national guidelines and related documents

These include:

- *Identification and Management of Familial Hypercholesterolaemia*, NICE clinical guideline 71, 2008[1]
- *The National Audit of the Management of Familial Hypercholesterolaemia 2010*, Royal College of Physicians[18]
- *Primary Care Service Framework: Familial Hypercholesterolaemia*, Primary Care Commissioning, 2010[31]
- *Model of Care: Familial Hypercholesterolaemia*, Western Australia Program Committee, 2008[6]
- *Familial Hypercholesterolemia: Screening, Diagnosis and Management of Paediatric and Adult Patients*, National Lipid Association Expert Panel on Familial Hypercholesterolemia, 2008[32]
- *Screening for Lipid Disorders in Children*, US Preventive Services Task Force, 2007.[33]

Description of technologies under assessment

Elucigene FH20™ (Gen-Probe Life Sciences, UK) and LIPOchip® (Progenika Biopharma, Spain) have been designed to reduce the need for CGA for the detection of genetic mutations associated with FH. These kits detect fewer genetic mutations than CGA.

TABLE 4 Estimate of the cost implications of NICE guideline CG71

Recurrent costs	Year 1 (£M)	Year 2 (£M)	Year 3 (£M)	Year 4 (£M)	Year 5 (£M)	Year 6 (£M)	Year 7 (£M)	Year 8 (£M)	Year 9 (£M)	Year 10 (£M)
Cascade testing	4.73	4.73	4.73	4.73	4.73	4.73	4.73	4.73	4.73	4.73
Drug therapy for people diagnosed with FH	2.55	5.11	7.66	10.21	12.76	15.31	17.86	20.41	22.96	25.51
Specialist referrals for people diagnosed with FH through cascade testing	0.69	0.69	0.69	0.69	0.69	0.69	0.69	0.69	0.69	0.69
Annual review meetings	0	0.60	1.19	1.79	2.39	2.99	3.59	4.19	4.79	5.39
Coronary events avoided	–0.45	–0.91	–1.36	–1.8	–2.25	–2.7	–3.15	–3.6	–4.05	–4.5
Net resource impact of guideline	7.52	10.22	12.91	15.62	18.32	21.02	23.72	26.42	29.12	31.82

Source: NICE costing template for CG71.[1]

Summary of Elucigene FH20

The Elucigene FH20 kit detects 20 genetic mutations associated with FH commonly found in the UK population. These mutations, with a frequency ranging from 1.3% to 11.4%, were identified from a cohort study in the UK involving 400 patients with FH.[26] Of these 20 mutations, 18 are found in the *LDLR* gene and one each in the *APOB* and *PCSK9* genes (*Table 5*).

The kit uses ARMS™ (AstraZenera, UK) allele-specific amplification technology, which detects point mutations, insertions or deletions in the *LDLR*, *APOB* and *PCSK9* genes in human whole blood. The principle of ARMS technology is that oligonucleotides with a 3′ mismatched residue will not function as polymerase chain reaction (PCR) primers under specified conditions. Selection of appropriate oligonucleotides allows specific mutant or normal DNA sequences to be amplified and detected by fluorescent analysis using capillary electrophoresis (a technique for separating substances from a fluid substrate). Elucigene FH20 can also be processed using gel-based analysis. The gel-based version is currently the only version available in the UK.

Mutations detected in the Elucigene FH20 assay are believed to be pathogenic; in other words, if the individual tests positive on the Elucigene FH20 kit, they have a confirmed diagnosis of FH.

A limitation of the kit is that it tests for only 20 genetic mutations associated with FH commonly found in the UK population. Hence, less frequently occurring FH-causing mutations will not be detected. Worldwide, approximately 1400 FH-causing mutations have been identified,[14] of which over 200 have been reported in the UK population. Therefore, in terms of the number of different FH-causing mutations found in the UK population, Elucigene FH20 would detect only around 10% of them.

Summary of LIPOchip

LIPOchip is a genetic test that uses DNA array technology as part of a tiered system (LIPOchip platform). The current version (version 10) of the chip tests for 189 mutations in the three principal genes causing FH, i.e. *LDLR*, *APOB* and *PCSK9*, known to occur in the UK population. The chip is designed to detect both point mutations and copy number changes of the *LDLR* gene that are associated with FH. The LIPOchip platform involves the following steps:

1. Samples are analysed using the DNA array system, which is designed to detect targeted mutations in the *LDLR*, *APOB* and *PCSK9* genes as well as copy number variations.
2. If these mutations are not detected the samples are fully sequenced for the mutations in the *LDLR* gene.

To process the chip, a thermal cycler, hybridisation station 4800™ (Tecan, Switzerland) and a glass-slide scanner are required. The data are analysed by the LIPOchip software, which generates a report containing information on the pathogenicity of detected mutations based on either scientific publications or bioinformatics analysis.

The manufacturer of LIPOchip also offers a sample testing service in its laboratory in Spain. The laboratory has achieved ISO 9001:2008 certification. Two processing options are available.

TABLE 5 Familial hypercholesterolaemia genetic mutations detected by Elucigene FH20

Gene	Mutation
LDLR	P664L, L458P, R329X, E207X, D200G, E80K, IVS3+1G>A, D461H, ΔG197, fs206, Q363X, W66G, V408M, D206E, C656R, K290RfsX20, C163Y, D461N
APOB	R3500Q
PCSK9	D374Y

The first is to run the LIPOchip test only (as described in step 1 above). The second runs the LIPOchip test and, in addition, for samples that are negative for a mutation after the LIPOchip test, carries out automated sequencing of the 18 exons of the *LDLR* gene (as described in steps 1 and 2 above). If step 2 fails to detect any mutations then the sample is confirmed as FH negative by the manufacturer.

Comparators

Low-density lipoprotein cholesterol concentration measurement (Simon Broome criteria)

Low-density lipoprotein cholesterol is most commonly assessed using an estimated figure calculated from the TC and high-density lipoprotein (HDL) cholesterol values and the triglyceride level, the combination commonly being referred to as 'lipids'. Because triglyceride measurements vary with fasting status, assessments are usually performed after an overnight fast. LDL-C by itself is neither fully sensitive nor specific for the diagnosis of FH, with considerable overlap between FH and non-FH individuals. LDL-C assessment would be recommended whether or not a genetic test is being undertaken, as other hyperlipidaemias (and the small proportion, perhaps around 5%, of patients with gene-negative FH) would have to be managed on the basis of lipid analysis, and the response to treatment would also be gauged by measuring lipids.

Comprehensive genetic analysis

Comprehensive genetic analysis is defined as the most complete genetic analysis generally available for FH within a diagnostic setting and is expected to detect almost all known FH-causing mutations. This analysis includes DNA sequence analysis of the promoter, all exons and the exon/intron boundaries and into the 3′ untranslated region of the *LDLR* gene, which will detect the majority (around 88%) of detectable FH mutations, MLPA for each exon and the promoter region of the *LDLR* gene to detect deletions and duplications (around 5% of detectable FH mutations) plus analysis for the common *APOB* p.Arg3527Gln gene mutation (around 5% of FH mutations) and the *PCSK9* p.Asp374Tyr gene mutation (around 2% of FH mutations).

Targeted gene sequencing

Targeted gene sequencing is used to describe the genetic test for sequencing a specific part of the gene where the family mutation is found. Targeted gene sequencing may be used for cascade testing to identify FH in the biological relatives of index cases.

Identification of important subgroups

There are few data on mutation frequencies in different ethnic groupings across the UK. Extrapolation from genetic studies of a range of other diseases would suggest that it is likely that mutation frequencies could vary markedly between different ethnic groups.

Current usage in the NHS

At present, because of current NHS commissioning arrangements for genetic tests and in common with much specialist genetic testing across the UK, only a small number of laboratories offer genetic testing for FH. As a result, the main test currently used to diagnose FH is measurement of LDL-C concentration. Those laboratories that do offer genetic testing for FH include hospitals in Aberdeen, Belfast, Birmingham, Bristol, Cardiff, Great Ormond Street and Salisbury. Most laboratories proceed straight to CGA rather than using a pre-screen, and most perform MLPA in addition to DNA sequencing.

UK national audit of the management of familial hypercholesterolaemia

Following the publication of the NICE guideline for FH in 2008,[1] a national clinical audit investigating the care received by individual patients with FH was undertaken by the Royal

College of Physicians, with the results published in 2010.[18] A 2008 survey had shown that around 15,000 adults and 500 children were being managed in UK lipid clinics and the audit examined around 15% ($n = 2324$) of the adults and 30% ($n = 147$) of the children.[34]

The results, key findings and recommendations of the audit in relation to cascade and DNA testing are detailed below.

Results

- A total of 42% of sites reported having no database for FH patients.
- Only 12% of sites had a commissioned cascade testing service.
- Only 15% of sites received NHS funding for DNA testing.
- In individuals in whom DNA testing was carried out, a mutation was detected in 62% of adults and 65% of children.
- When the family mutation was known the child had been offered a DNA test in 94% of cases.

Key findings

- Current resources were inadequate to cope with the identification of the predicted FH relatives of affected cases UK-wide. This included access to trained staff (86% of sites had no lipid specialist nurses), IT provision and pedigree drawing.
- There was a major lack of family 'cascade' testing, whether carried out on the basis of lipid levels or, more effectively, of a DNA diagnosis.
- Although there was good access to DNA diagnosis and funding for DNA testing in Scotland, Northern Ireland and Wales, access in England was poor.

Key recommendations

- Additional resources would be needed to cope with the care of new FH patients identified by cascade testing. Training to address the shortage of staff with key skills would be required.
- Systems needed to be developed and implemented to carry out comprehensive 'cascade' testing. This would require trained health professionals with the appropriate skills to follow up the families of index patients, improved IT resources, including a FH patient database, and pedigree drawing.
- Resources were needed for DNA diagnosis and clinical genetics input.
- Based on published data, cascade testing alone would find < 50% of the predicted 100,000 unidentified FH patients in the UK, and other methods for finding FH index cases would need to be explored.
- Given that FH families were geographically dispersed, cascade testing might be facilitated by a specifically funded UK FH Register to which all FH cases would be notified.

Anticipated costs associated with the intervention(s)

Diagnostic technologies

With regards to genetic tests, two novel screening techniques have emerged (Elucigene FH20 and LIPOchip). Some reports suggest that DNA testing for FH costs approximately £400, whereas other work estimates that the process could cost between £500 and £1000 per test. The main reasons for the large variation in reported costs are (1) the definition of DNA testing has varied in previous reports with differences in the genes sequenced and whether or not genes were screened for deletions or duplications and (2) the cost of DNA sequencing has reduced over time as laboratories build up economies of scale and improve equipment allowing for faster processing and reporting times; as a result, previous cost estimates for testing for FH have varied greatly across reports and studies.

The Elucigene FH20 kit is available at a cost of £15 per test and LIPOchip is available at a cost of €250 or approximately £198. However, these costs do not account for staff time to process

samples, consumables or overheads. Therefore, the costs of Elucigene FH20 and LIPOchip will be much greater in practice than just their unit test cost.

A standard NHS tariff does not exist per se for genetic tests; however, a recently developed system is now increasingly used by genetics laboratories across the UK to apportion costs to genetic testing services. This 'MOLU' (MOLecular Units) pricing system is the most commonly used costing mechanism for genetic testing of FH in laboratories across the UK. Genetic testing strategies vary in complexity depending on the type and volume of analysis required for different reports (genetic tests). The PCR amplicon or equivalent was chosen as a measure of complexity, which is transparent and easily counted. Reports are grouped into a total of six 'bands' (A–F). Bands are assigned and given a weighting according to the number of amplicons analysed to produce a report in that band. The number of reports multiplied by the appropriate band weight produces a final number of MOLUs. The total number of MOLUs derived from the exercise can be divided into the total laboratory budget to give an approximate monetary value to MOLUs. This in turn produces an indicative cost for the various testing strategies. Laboratories that can keep their budget constant or can reduce it but increase the number of MOLUs produced will have lower unit costs. It is estimated that the average cost per MOLU is between £30 and £35. Costs of all genetic tests including targeted gene sequencing for relatives can be estimated in this way.

Although the MOLU costing approach has been decided upon as the most appropriate and generally accepted method to cost these test strategies, it is far from ideal. The approach does not necessarily account for full economic costing or indeed opportunity costs of resources. The MOLU approach is basically a price banding agreed upon in collaboration between the laboratories from a UK Genetic Testing Network (UKGTN) group and the Clinical Molecular Genetics Society (CMGS). This has limitations in terms of the accuracy of the costs produced; however, in the absence of any more robust costing methods for these genetic tests, the MOLU classification system has been deemed the most appropriate method with which to compare these testing strategies.

Costs of LDL-C measurement will need to take into account the costs of resource use to retrieve samples and the costs of testing the samples by a laboratory. LDL-C testing is relatively inexpensive compared with genetic testing. These assays are performed routinely in most laboratories using current fully automated equipment (e.g. the laboratory in Aberdeen Royal Infirmary performs > 100,000 per annum) and the reagent cost is minimal (pence), so the overall cost of the procedure consists almost entirely of the general costs associated with processing any sample (around £3–10).

Ancillary costs

The genetic equipment required to process the tests is assumed to be readily available in UK laboratories. However, should this not be the case as standard, the costs of one-off purchases of this equipment will be included in the laboratory budget and thus indirectly accounted for using the MOLU system identified above.

Treatments

As per recommendations from NICE clinical guideline CG71,[1] the recommended treatment for patients with FH is high-intensity statin therapy (usually atorvastatin 80 mg). For patients at risk of CHD based on high lipid levels but who do not have FH, the recommended treatment is low-intensity statin therapy (e.g. simvastatin 40 mg). The cost of atorvastatin is due to decrease during the course of this assessment and is likely to be equivalent to that of generic simvastatin. The implications of this are explored in the cost-effectiveness analysis. Costs of a number of other statin-based therapies such as rosuvastatin, pravastatin, etc. are considered. Other treatments include ezetimibe (evidence of efficacy uncertain) and bile acid sequestrants (costly).

Other costs

Other cost considerations include the cost of health-care professionals to identify family pedigree and the costs of initiating contact with relatives for cascade testing. Costs of annual follow-ups for patients diagnosed with FH are also considered in the analysis.

Care pathways

The care pathway for this evaluation is determined by NICE clinical guideline CG71[1] on the identification and management of FH. The key elements from the care pathway are as follows:

- A diagnosis of FH should be made on the basis of a combination of the Simon Broome criteria for a clinical diagnosis and a DNA test to confirm this diagnosis unequivocally. This confirmation should include two measures of LDL-C because of biological and analytical variability of the tests.
- The children of adults identified with FH should be offered a DNA test if the family mutation is known; alternatively, if the mutation is unknown, LDL-C testing should be carried out and repeated after puberty.
- Cascade testing of at-risk relatives is recommended using a combination of DNA testing and LDL-C concentration measurement in first-, second- and possibly third-degree biological relatives. If the family mutation is known then DNA testing and not LDL-C should be used to identify relatives.
- Prescription of a high-intensity statin should be considered to achieve a recommended reduction in LDL-C concentration of > 50% for patients with FH. Lipid-modifying treatment in children with FH should be considered by age 10 years and initial treatment should be statin therapy.

It is important to note that, in practice, the guideline is not very well implemented across the UK because of a lack of funding for the genetic testing of patients with FH and cascade genetic testing of identified relatives. In many cases, LDL-C is the most commonly administered test to identify FH but is subject to poor accuracy and reliability.

Definition of the decision problem

Purpose of the decision to be made

The purpose of this assessment is to address the following questions:

1. What are the most effective and cost-effective strategies for confirming a diagnosis of FH in index cases and for cascade testing of relatives?
2. In cascade testing of relatives for mutations identified in index cases by Elucigene FH20 or LIPOchip, would it be more cost-effective to use those tests rather than targeted gene sequencing?

Definition of the intervention

The interventions are described in *Description of technologies under assessment*.

Populations and relevant subgroups

Populations and relevant subgroups are described in *Chapter 2*, *Inclusion and exclusion criteria*.

Place of the interventions in the treatment pathway(s)

The care pathway for this assessment is based on NICE clinical guideline CG71[1] on the identification and management of FH.

Index cases

The assessment investigates the use of diagnostic strategies including Elucigene FH20 and/or LIPOchip for providing an unequivocal diagnosis of FH for those with a clinical diagnosis based on the Simon Broome criteria.

Cascade testing of relatives

The assessment investigates the use of diagnostic strategies including Elucigene FH20 and LIPOchip for cascade testing to identify FH in the relatives of index cases. The use of Elucigene FH20 or LIPOchip for cascade testing depends on the mutation detected in the index case and the cost of targeted gene sequencing. (In index cases with an identified genetic mutation, targeted gene sequencing is also considered for cascade testing of relatives. In index cases without an identified genetic mutation, cascade testing using LDL-C concentration measurement is considered.)

A scenario encompassing a single test strategy (Elucigene FH20 or LIPOchip) that does not end in CGA for test-negatives may not detect all cases of FH. In such a scenario there may be implications for test-negative patients in terms of how their condition is managed.

Relevant comparators

Relevant comparators are described in *Description of technologies under assessment*.

Overall aim and objectives of the assessment

The overall aim of the assessment is to assess the diagnostic accuracy, effect on patient outcomes and cost-effectiveness of Elucigene FH20, LIPOchip and comparators for the diagnosis of FH.

The objectives of the assessment are to:

- systematically review the evidence on the test performance and clinical effectiveness of Elucigene FH20, LIPOchip and comparators in confirming a diagnosis of FH in patients with a clinical diagnosis of FH
- systematically review the evidence on the test performance and clinical effectiveness of Elucigene FH20, LIPOchip and comparators in cascade testing of relatives of index cases with a confirmed diagnosis of FH
- review the evidence on the cost-effectiveness of Elucigene FH20 and LIPOchip for the identification of index cases and cascade testing of relatives
- estimate the costs of different diagnostic strategies for detecting FH in index cases and for cascade testing of relatives of index cases with a diagnosis of FH
- develop a comprehensive health economic model to link test accuracy of various diagnostic testing strategies to lifelong cost and treatment outcomes using a linked evidence approach to the modelling process
- determine the most cost-effective testing strategy relative to current practice (LDL-C) and also to investigate which strategies may be cost-effective compared with current NICE guideline recommendations (i.e. DNA testing), akin to CGA in the context of this assessment.

Chapter 2

Assessment design and results: test performance

Methods for reviewing test performance

Identification of studies

Studies were identified by searching electronic databases and relevant websites, contact with experts in the field and the scrutiny of bibliographies of retrieved papers. Highly sensitive electronic searches were conducted to identify reports of published and ongoing studies on the diagnostic accuracy and clinical effectiveness of tests for FH in index cases and for cascade testing of relatives. The search strategy excluded studies published before 2000.

The databases searched were MEDLINE (1948 to Week 1 2011), MEDLINE In-Process & Other Non-Indexed Citations (10 January 2011), EMBASE (1980 to 2011 Week 1), BIOSIS (1956 to 10 January 2011), Science Citation Index (1970 to 10 January 2011), Conference Proceedings Citation Index – Science (1990 to 10 January 2011) and Cochrane Controlled Trials Register (The Cochrane Library, Issue 1, 2011), as well as current research registers: Current Controlled Trials (January 2011), Clinical Trials (January 2011) and the World Health Organization International Clinical Trials Registry (January 2011). Additional databases searched for systematic reviews and other background information included the Cochrane Database of Systematic Reviews (The Cochrane Library, Issue 1, 2011), Database of Abstracts of Reviews of Effects (January 2011) and Health Technology Assessment database (January 2011). Recent conference proceedings were also searched. Full details of the search strategies used and websites consulted are documented in *Appendix 3*. In addition, reference lists of all included studies were scanned to identify additional potentially relevant studies.

Inclusion and exclusion criteria

Population

The population considered was adults and children with a clinical diagnosis of FH (the index cases/probands) based on the Simon Broome, Dutch or MedPed criteria and, for cascade testing, the first-, second- and third-degree biological relatives of the index case. (In the protocol for the review we stated that we would consider those with a clinical diagnosis based on the Simon Broome criteria as recommended for clinical diagnosis of FH in the UK. However, we also identified a few studies based on the Dutch and MedPed criteria and in consultation with our clinical advisers we relaxed our inclusion criteria to also include studies in which participants had received a clinical diagnosis of FH based on these criteria, as clinical advice suggested that these criteria were sufficiently similar to the Simon Broome criteria and if consistently applied would also provide potentially useful evidence.)

Given sufficient evidence, subgroup analysis was to be undertaken on the performance of Elucigene FH20 and LIPOchip in ethnic populations.

Setting

The settings considered were secondary or tertiary care.

Interventions and comparators

The interventions considered were Elucigene FH20 and LIPOchip for index cases and cascade testing of relatives. The comparators considered for testing in index cases were (1) CGA and (2) LDL-C concentration measurement (Simon Broome, Dutch or MedPed criteria). The comparators considered for cascade testing of relatives were (1) targeted gene sequencing and (2) LDL-C concentration measurement (age- and gender-specific criteria as recommended in NICE clinical guideline CG71[1]).

Reference standard

The reference standard was CGA in combination with the Simon Broome, Dutch or MedPed criteria. CGA was defined as the 'most complete genetic analysis' generally available for FH within a diagnostic setting and is expected to detect almost all known FH-causing mutations. This analysis includes DNA sequence analysis of the promoter, all exons and the exon/intron boundaries and into the 3′ untranslated region of the *LDLR* gene, which will detect the majority (~88%) of detectable FH mutations, MLPA for each exon and the promoter region of the *LDLR* gene to detect deletions and duplications (~5% detectable FH mutations) plus analysis for the common *APOB* p.Arg3527Gln gene mutation (~5% of FH mutations) and the *PCSK9* p.Asp374Tyr gene mutation (~2% of FH mutations).

During the screening process it was ascertained that some studies reporting genetic analysis did not fulfil all of the above criteria for CGA, for example:

- *LDLR*, *APOB* and *PCSK9* gene analysis but testing for deletion/duplication was carried out using a process other than MLPA such as Southern blot analysis or quantitative multiplex PCR methodology (QMFSP)
- *LDLR* and *APOB* gene analysis, but no *PCSK9* analysis.

Therefore, we took a pragmatic decision to still include studies reporting such an 'incomplete CGA' and to assess the quality of such a reference standard in terms of comprehensiveness and variations in test accuracy.

Studies reporting the following single genetic analyses were excluded:

- *APOB* gene analysis only
- *PCSK9* gene analysis only
- test for deletion/duplication only.

In the event of a sequential mutational detection strategy used for the diagnosis of FH, for example Elucigene FH20 followed by gene sequencing for those negative on Elucigene FH20 and then followed by MLPA tests for those negative on gene sequencing, the combination of these sequences could be considered to be CGA.

Low-density lipoprotein cholesterol measurement as part of the clinical diagnosis was one of the comparators. Estimates of the accuracy of LDL-C using the reference standard of CGA plus a clinical diagnosis that includes LDL-C measurement are likely to be inflated compared with the estimates of accuracy of other index tests being evaluated. Therefore, for inclusion of studies reporting the diagnostic accuracy of LDL-C (which is a part of the clinical diagnosis), we considered the estimates of accuracy of LDL-C against a reference standard of CGA (either most complete or incomplete) only.

Outcomes

The following outcomes were considered:

- test accuracy: sensitivity, specificity, positive likelihood ratio and negative likelihood ratio.

In any studies reporting the above outcomes the following outcomes were also considered:

- proportion of cases with an unequivocal diagnosis identified by Elucigene FH20 and LIPOchip
- proportion requiring CGA after Elucigene FH20 and LIPOchip
- proportion of FH identified from cascade testing
- acceptability of the tests
- interpretability of the tests.

Test accuracy data on the absolute numbers of true-positives, false-positives, false-negatives and true-negatives were extracted or calculated from the information provided in the studies. We also considered studies in which derivation of a complete 2×2 diagnostic table was not possible but which reported data to allow derivation of one of the test accuracy measures, for example sensitivity but not specificity.

Study design

The following types of studies were considered:

- direct (head-to-head) studies in which the index test, comparator test and reference standard test were carried out independently in the same group of people
- randomised controlled trials (RCTs) in which people were randomised to the index and comparator test(s) and all received the reference standard test.

In case of insufficient evidence from direct and randomised studies, indirect (between-study) comparisons in the following types of study were also considered:

- diagnostic cross-sectional studies comparing the index test or comparator test against a reference standard test
- case–control studies in which two groups were created, one known to have the target disease and one known not to have the target disease, in which it was reasonable for all included to go through the tests.

Exclusion criteria

The following types of reports were excluded:

- preclinical and biological studies
- reviews, editorials and opinions
- case reports
- reports investigating technical aspects of a test.

Non-English-language reports were excluded.

Data extraction strategy

Two reviewers (PS and GM) independently screened the titles and abstracts of all reports identified by the search strategy. Full-text copies of all studies deemed to be potentially relevant were obtained and two reviewers (PS and GM) independently assessed them for inclusion. Disagreements were resolved by consensus or arbitration by a third party (ZM and WS).

A data extraction form was developed and piloted (see *Appendix 4*). One reviewer (PS) extracted the details of study design, participants, index, comparator, reference standard tests and outcome data. A second reviewer (GM) checked the data extraction. Any disagreements were resolved by consensus or arbitration by a third party (ZM and WS). Any study data requested and received from the manufacturers that met the inclusion criteria were to be extracted and quality assessed in accordance with the procedures outlined in the protocol for the assessment.

Quality assessment strategy

The methodological quality of the included diagnostic studies was assessed using QUADAS,[35] a quality assessment tool developed for use in systematic reviews of diagnostic studies. QUADAS was developed through a formal consensus method and was based on empirical evidence. The checklist was adapted for the purposes of this review (it is designed to be adapted to make it more applicable to a specific review topic) (see *Appendix 5* for the modified QUADAS checklist). The original QUADAS checklist contained 14 questions. Questions 1, 3, 5–7 and 10–14 of the original QUADAS tool were retained (questions 1–10 in the modified version). Three questions in the original QUADAS tool that related to the quality of reporting rather than methodological quality were omitted from the modified version (questions 2, 8 and 9). These questions related to the description of (1) the selection criteria, (2) the execution of the index test and (3) the execution of the reference standard test. A fourth question relating to whether or not the time period between the reference standard and index test was short enough to be reasonably sure that the target condition did not change between the two tests was also omitted. This question was not considered to be relevant as a person will either have or not have FH.

Three questions were added to the modified checklist on (1) whether or not cut-off values were established before the study was started, (2) whether or not the technology of the index test was unchanged since the study was carried out and (3) whether or not the study provided a clear definition of what was considered to be a 'positive' result. Three questions in the modified checklist were considered to be relevant to studies reporting LDL-C but not applicable to studies reporting Elucigene FH20 or LIPOchip owing to the nature of these tests: question 8, 'Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?'; question 11, 'Were cut-off values established before the study was started?'; and question 13, 'Did the study provide a clear definition of what was considered to be a "positive" result?'.

Two reviewers independently assessed the quality of all included full-text diagnostic studies using the modified version of QUADAS. Each question was checked as 'yes', 'no' or 'unclear', or, for questions 8, 11 and 13, 'not applicable' for reports of Elucigene FH20 or LIPOchip. Any disagreements were resolved by consensus or arbitration by a third party. Studies were not included or excluded on the basis of their methodological quality. Conference abstracts were not quality assessed on the basis that they were not considered to contain sufficient information to allow for an adequate assessment of their methodological quality.

Data analysis

Analysis focused on the ability of Elucigene FH20, LIPOchip and its comparators to confirm FH in index cases of FH diagnosed clinically. Two-by-two tables were extracted from each of the included studies in which information was provided on the numbers of true- and false-positives and -negatives for the index and/or comparator test compared with the reference standard for detecting those mutations that the index and/or comparator test are designed to identify. For each study, where there was sufficient information, sensitivity, specificity, positive and negative likelihood ratios and their confidence intervals (CIs) were calculated.

Where appropriate and given sufficient information, we had planned to use summary receiver operating characteristic (SROC) curves for the meta-analysis of data from studies reporting estimates of true- and false-positives and -negatives. Where appropriate, it was planned to fit models using the hierarchical summary receiver operating characteristic (HSROC) framework, which takes proper account of the diseased and non-diseased sample sizes in each study, and allows estimation of random effects for the threshold and accuracy effects, and testing of the impact of potential sources of heterogeneity. However, there was insufficient information to enable pooling of results or to provide SROC curves as planned and so forest plots of sensitivity and specificity were used to visualise the heterogeneity amongst the included studies. No formal meta-analysis was therefore carried out.

Diagnostic accuracy metrics

For the purpose of this assessment, we define test-positive and test-negative as follows:

- Elucigene FH20/LIPOchip tests: those with a FH-causing mutation detected by Elucigene FH20 or LIPOchip were defined as 'test-positive' and those with no mutations detected were defined as 'test-negative'.
- LDL-C tests (as a part of the Simon Broome criteria): we assumed that people with positive clinical criteria would have positive cut-offs of LDL-C as suggested in the definition of the criteria. A minimum LDL-C level of 4 mmol/l is required to diagnose index cases.
- Age- and gender-specific LDL-C test (as recommended in NICE guideline): those with LDL-C levels greater than the cut-offs were defined as 'test-positive' and those with LDL-C levels lower than the cut-offs were defined as 'test-negative'.
- True-positives: people with clinical FH who are positive on tests (Elucigene FH20 or LIPOchip or LDL-C as part of the Simon Broome criteria or age- and gender-specific LDL-C) and positive on CGA.
- False-negatives: people with clinical FH who are negative on tests, but positive on CGA.
- False-positives: people with clinical FH who are positive on tests, but negative on CGA.
- True-negatives: people with clinical FH who are negative on tests and negative on CGA.
- Sensitivity = true-positive/(true-positive + false-negative) × 100.
- Specificity = true-negative/(true-negative + false-positive) × 100.

Results of test performance

Quantity of research available

Quantity of studies identified

The searches identified 1529 records for the review of test performance. Following screening of titles and abstracts, 1296 articles were excluded and full-text reports of the remaining 233 articles were obtained for further assessment. *Figure 3* shows a flow diagram outlining the screening process.

Appendix 6 lists the 15 studies (17 reports) that were included in the review of test performance (*Table 6* lists the studies, tests evaluated, publication status and other linked reports). Of the 15 studies, three (four reports) reported Elucigene FH20,[36–38] five (six reports) evaluated LIPOchip,[39–43] four reported LDL-C compared with genetic analysis[44–47] and three reported age- and gender-specific LDL-C for cascade testing of relatives.[48–50] We did not identify any studies reporting a combination of the index tests, that is Elucigene FH20 and LIPOchip.

Number and type of studies excluded

A list of the 221 potentially relevant studies identified by the search strategy for which full-text papers were obtained but which subsequently failed to meet the inclusion criteria is given in *Appendix 7*.

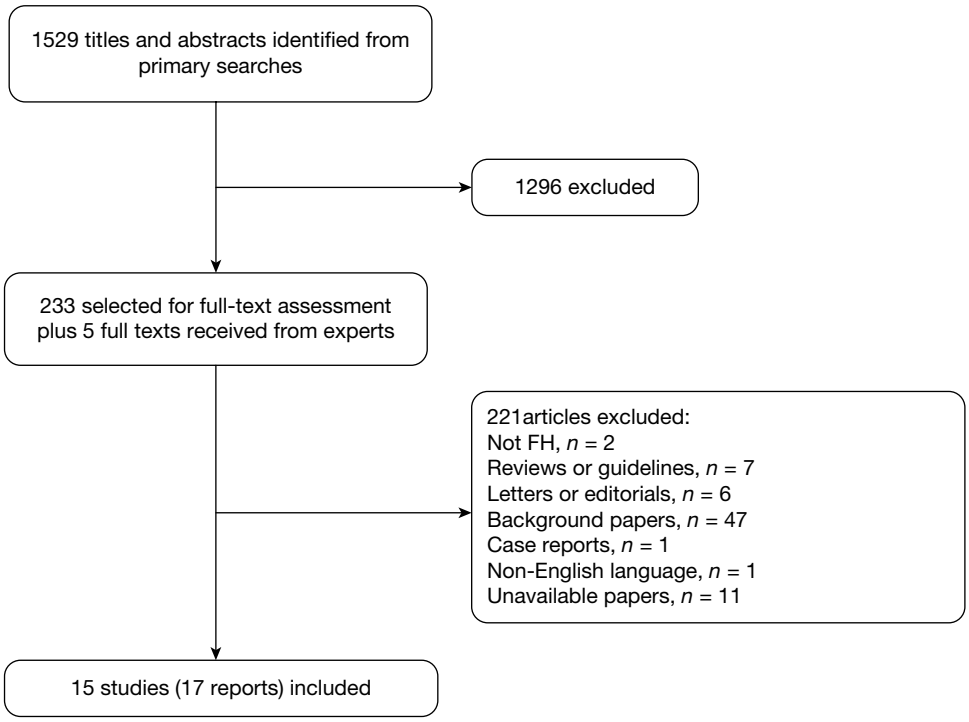

FIGURE 3 Flow diagram outlining the screening process.

TABLE 6 Summary of included studies

Main study[a]	Test(s) evaluated	Publication status	Other reports linked to the study (not included in the review)
Alonso 2009[39]	LIPOchip	Full text	
Callaway 2010[40]	LIPOchip	Presentation plus information from author	
Civeira 2008[44]	LDL-C	Full text plus information from author	
Damgaard 2005[45]	LDL-C, targeted sequencing	Full text	
Hooper 2009[36]	Elucigene FH20	Abstract	
Lee 2010[48]	LDL-C age and gender specific (NICE criteria)	Abstract and information from author	
Mabuchi 2005[46]	LDL-C	Full text	Yu 2002[51]
Palacios 2010[41] [Stef 2010[52]]	LIPOchip	Abstract and poster plus manufacturer data	
Starr 2008,[49] Damgaard 2005[45]	LDL-C age and gender specific (NICE criteria), targeted sequencing	Full text	Leren 2004,[53] Umans-Eckenhausen 2001[19]
Stef 2009[42]	LIPOchip	Abstract	
Taylor 2010[37] [Taylor 2007[54]]	Elucigene FH20, targeted sequencing	Full text plus information from author	Taylor 2009,[28] Tabrah 2005[55]
Tejedor 2005[43]	LIPOchip	Full text	Tejedor 2006,[56] Oliva 2009[57]
Widhalm 2007[47]	LDL-C	Full text	
Wiegman 2003[50]	LDL-C age specific, targeted sequencing	Full text	Fouchier 2001[58]
Yarram 2010[38]	Elucigene FH20, cascade test	Presentation	

Reports in square brackets are secondary reports.

Characteristics of the included studies

Appendix 8 shows the characteristics of the individual included studies.

Study design

All of the studies were diagnostic cross-sectional studies evaluating the performance of Elucigene FH20,[36–38] LIPOchip[39–43] or LDL-C[44–50] against a reference standard of genetic analysis (either incomplete or complete in terms of the definition of CGA as stated in *Inclusion and exclusion criteria*) in which all participants received a clinical diagnosis using Simon Broome, Dutch or MedPed criteria. No RCTs were identified that randomised participants to any of the tests of interest with all receiving a reference standard test.

Country and setting

Of the eight studies evaluating Elucigene FH20 or LIPOchip, four were conducted in the UK[37,38,40,41] (two[37,38] reporting Elucigene FH20 and two[40,41] reporting LIPOchip) and one was conducted in Australia[36] (evaluating Elucigene FH20), with the remaining three taking place in Spain[39,42,43] (all of which reported LIPOchip). Of the seven studies reporting the performance of LDL-C (in index cases or for cascade testing of relatives), one each was conducted in the UK,[48] Spain,[44] Denmark,[45] Austria,[47] Japan[46] and the Netherlands.[50] The study by Starr and colleagues[49] included participants from the Netherlands, Denmark and Norway. When reported (seven studies), the clinical diagnosis was performed in lipid clinics.

Clinical diagnosis

The clinical diagnostic criteria used tended to differ according to the country where the study was carried out. The studies by Palacios and colleagues,[41] Callaway and colleagues,[40] Taylor and colleagues,[37] Yarram[38] and Lee and colleagues[48] were conducted in the UK and their participants had a clinical diagnosis based on the Simon Broome criteria. Of three studies set in Spain, those by Stef and colleagues[42] and Alonso and colleagues[39] used the Dutch criteria, whereas the study by Tejedor and colleagues[43] employed the MedPed criteria. The study by Hooper and colleagues,[36] set in Australia, used the Dutch criteria whereas the study by Widhalm and colleagues,[47] set in Austria, used the MedPed criteria.

In the studies by Civeira and colleagues[44] and Damgaard and colleagues[45] patients were given a clinical diagnosis followed by a genetic diagnosis and were then retrospectively classified by the Simon Broome, Dutch and MedPed criteria. Civeira and colleagues[44] used an initial clinical diagnosis based on the MedPed criteria, whereas Damgaard and colleagues[45] included participants who fulfilled two of the following three criteria: (1) LDL-C > 6 mmol/l, TC > 8 mmol/l and triglycerides < 2.5 mmol/l; (2) tendon xanthomata; and (3) a history of coronary artery disease before the age of 60 years in the patient and/or in a first-degree relative and/or hypercholesterolaemia in a first-degree relative.

In the studies by Starr and colleagues[49] and Mabuchi and colleagues[46] a genetically tested cohort of relatives was recruited to study the test performance of age- and gender-specific LDL-C cut-offs and a cut-off of 4 mmol/l, which is the minimum cut-off required by Simon Broome criteria respectively. In the study by Starr and colleagues, clinically diagnosed index cases based on the Dutch criteria (the Netherlands) and a combination of lipid levels, clinical characteristics and family history (Norway and Denmark) were included, whereas the study by Mabuchi and colleagues[46] included clinically diagnosed index cases based on TC (≥ 5.9 mmol/l and < 12.9 mmol/l) with tendon xanthomata or primary hypercholesterolaemia with/without tendon xanthomata in a family with FH patients among first-degree relatives. The study by Wiegman and colleagues[50] recruited relatives of index cases with a clinical diagnosis of FH based on the MedPed criteria or from a genetic diagnosis.

Participants

In the studies by Taylor and colleagues,[37] Damgaard and colleagues,[45] Mabuchi and colleagues,[46] and Tejedor and colleagues[43] the participants were all adults. In the study by Wiegman and colleagues[50] the participants were children. In the studies by Starr and colleagues[49] and Widhalm and colleagues[47] the participants were a mixture of adults, adolescents and children, whereas in the study by Civeira and colleagues[44] they were adults and adolescents. The remaining seven studies[36,38–42,48] (six abstracts and one full text) did not specify whether the participants (index patients or relatives) were adults, children or adolescents.

Eight studies reported diagnostic accuracy in index cases only,[36,39–44,46] whereas four[37,38,45,47] reported this information both for index cases and for cascade testing of relatives, with the remaining three studies[48–50] reporting test performance for cascade testing of relatives only. In studies reporting cascade testing of relatives these were all first-degree relatives apart from the two studies by Damgaard and colleagues[45] and Lee and colleagues,[48] in which this information was not specified.

For studies evaluating the test performance of Elucigene FH20 and LIPOchip, the sample size ranged from 22 patients[40] to 2462 patients.[42] In studies reporting test performance of LDL-C, the sample size ranged from 263[47] to 3294.[49] In studies reporting cascade tests through targeted sequencing the sample size of relatives ranged from 27 relatives (from 104 index cases)[38] to 1034 relatives (from 591 index cases).[50]

In the study by Lee and colleagues[48] all included relatives were heterozygous FH (coming from homozygous FH index cases), whereas in the study by Mabuchi and colleagues[46] none was homozygous. The rest of the studies did not report on the status of FH patients. Three studies[43–45] reported the number of participants at baseline with coronary artery disease, which ranged from 15% to 20%, and xanthomata, which ranged from 16% to 56%. The mean LDL-C concentration of participants as reported in two studies ranged from 4.3 mmol/l to 5.7 mmol/l.[47,49]

Only one study reported the proportion of participants by ethnic group.[37] In this study most of the patients were white British (85.4%), 5.8% were of European origin and very few were from ethnic minorities, including 1.7% of Middle Eastern origin, 4.5% of Indian-Asian origin, 1.3% of African or Afro-Caribbean origin and 0.8% from the Far East.

Characteristics of the tests reported by the included studies

Table 7 summarises the characteristics of the studies reporting Elucigene FH20 or LIPOchip, whereas *Table 8* summarises the characteristics of the studies reporting LDL-C.

Elucigene FH20

Three studies, by Taylor and colleagues,[37] Hooper and colleagues[36] and Yarram,[38] reported Elucigene FH20 (Gen-Probe, UK) as a pre-screen genetic tool for the diagnosis of FH. In all three studies, the genetic screening of clinically diagnosed patients took place in three stages of tests: (1) Elucigene FH20 to screen for 20 common genetic mutations found in the UK (18 *LDLR*, one *PCSK9*, one *APOB*); (2) MLPA to screen for deletions and duplications in the *LDLR* gene for those negative on Elucigene FH20; and (3) sequencing of the entire *LDLR* gene for those negative on MLPA. In the study by Taylor and colleagues[37] sequencing was performed using SSCP, denaturing high-performance liquid chromatography (dHPLC) and direct sequencing (promoter, all exons, the exon intron boundaries, 3′ untranslated region). Hooper and colleagues[36] reported exon-by-exon sequencing of the *LDLR* gene, whereas Yarram[38] reported sequencing of all 18 *LDLR* exons and the promoter region.

TABLE 7 Summary of the characteristics of studies reporting Elucigene FH20 or LIPOchip

Study, country	Study design, total sample (*n*)	Study population	Methods (number evaluated for each test)	Genes tested	Setting (prevalence of FH[a])
Elucigene FH20					
Taylor 2010[37] UK	Cross-sectional evaluation (consecutive), 635	Clinically diagnosed definite FH, possible FH or unclassified FH based on Simon Broome criteria First-degree relatives of index cases	Elucigene FH20 (635), SSCP/dHPLC/ sequencing (533), MLPA (414) Targeted sequencing of relatives (296)	*LDLR*, *APOB*, *PCSK9*	Six lipid clinics, laboratory in UK, one genetics laboratory (36.5%)
Hooper 2010[36] Australia	Cross-sectional evaluation, 63	Clinically diagnosed patients with definite FH based on Dutch criteria	Elucigene FH20 (63), MLPA (not reported), sequencing	*LDLR*, *APOB*, *PCSK9*	Not reported (77.8%)
Yarram 2010[38b] UK	Cross-sectional evaluation, 104	Clinically diagnosed definite FH, possible FH, unclassified FH or criteria unmet based on Simon Broome criteria	Elucigene FH20 (104), sequencing, MLPA (not reported) Cascade (27)	*LDLR*, *APOB*, *PCSK9*	One genetics laboratory in Bristol, UK (48%)
LIPOchip					
Alonso 2009[39] Spain	Cross-sectional comparative, 808	Clinically diagnosed patients with definite FH or probable FH based on Dutch criteria	LIPOchip platform (195 mutations): DNA array (808), QMFSP (389), sequencing (312)	*LDLR*, *APOB*,	Eleven lipid clinics, one genetics laboratory in Spain (66.5%)
Callaway 2010[40] UK	Cross-sectional comparative (validation study), 22	Clinically diagnosed definite FH based on Simon Broome criteria or cholesterol > 8 mmol/l plus family history of high cholesterol or cardiovascular disease (these were negatives on Elucigene FH20)	LIPOchip platform (251 mutations) (22) dHPLC/sequencing/MLPA (22) (All received Elucigene FH20, LIPOchip and sequencing/MLPA)	*LDLR*, *APOB*, *PCSK9*	One genetics laboratory in, Wessex, UK (not calculable)
Palacios 2010[41] UK	Cross-sectional comparative, 126	Clinically diagnosed patients with Simon Broome criteria and tested with Elucigene FH20 + SSCP/dHPLC/direct sequencing	LIPOchip platform (251 mutations): LIPOchip (126), sequencing (not reported) LIPOchip version 10 (UK) (126), data from manufacturer	*LDLR*, *APOB*, *PCSK9*	Two centres, one genetics laboratory in Spain (51.6%)
Stef 2009[42] Spain	Cross-sectional evaluation, 2462	Clinically diagnosed patients with Dutch–MedPed criteria	LIPOchip platform (247 mutations): LIPOchip (2462), sequencing (not reported)	*LDLR*, *APOB*, *PCSK9*	Not reported (49.0%)
Tejedor 2005[43] Spain	Cross-sectional comparative, 407 phenotyped, 1180 genotyped	Clinically diagnosed definite FH or probable FH based on Dutch–MedPed criteria (genotyped FH identified by SSCP/sequencing used to test performance of chip)	LIPOchip (118 mutations): DNA array (407), sequencing (123 with DFH) SSCP/sequencing (1180)	*LDLR*, *APOB*	Seventy lipid clinics, genetics laboratory (45.9%)

DFH, definite FH.

a Prevalence of FH represents the total FH diagnosed with genetic testing as a percentage of the total number in the study population in that setting.

b Yarram[38] also tested 18% (19/104) of patients who did not meet Simon Broome criteria.

Taylor and colleagues[37] and Yarram[38] included unrelated patients who were clinically diagnosed as having definite FH or possible FH based on the Simon Broome criteria. These studies also reported on clinical cases who could not be classified as having definite or possible FH because of insufficient information provided from the lipid clinics (usually because of missing untreated cholesterol data), grouped as unclassified FH. Additionally, Yarram[38] included 18% (19/104) of patients who did not met Simon Broome criteria in the analysis. Hooper and colleagues,[36] on the other hand, included patients with a diagnosis of definite FH based on the Dutch criteria who were enrolled in the FH Western Australia (FHWA) pilot programme.

A paper[54] relating to the study by Taylor and colleagues (for which Taylor and colleagues[37] is considered the primary reference) reported results on an earlier version of the Elucigene FH20 kit (Elucigene FH013 B1), which screened for 13 common genetic mutations found in the UK population (11 *LDLR*, one *PCSK9* and one *APOB*). Detection rate data from this test were included with those from Elucigene FH20 in the results reported by Taylor and colleagues[37] but were treated as if all samples had been tested with Elucigene FH20. Results from the Taylor and colleagues 2007 report[54] were included because all study participants received both Elucigene FH20 and also a reference standard of sequencing of the *LDLR* gene, unlike the Taylor and colleagues 2010 report,[37] in which only test-negatives on Elucigene FH20 went on to receive CGA.

Both of the studies by Taylor and colleagues[37] and Hooper and colleagues[36] reported, for index cases with a clinical diagnosis of FH, the detection rate using Elucigene FH20 as a pre-screening test alone and when used in combination with sequencing and MLPA. Yarram[38] reported the sensitivity of Elucigene FH20 against CGA. Taylor and colleagues[37] additionally reported detection rates for FH by ethnicity. The studies by Taylor and colleagues[37] and Yarram[38] also reported results for cascade testing of relatives, in which the index cases had been identified using Elucigene FH20 initially followed by genetic screening in the form of sequencing and then MLPA.

LIPOchip

Five studies evaluated various versions of the LIPOchip platform (Progenika Biopharma, Spain).[39–43] In two studies, by Palacios and colleagues[41] and Stef and colleagues,[42] the LIPOchip platform comprised detection of point mutations in the *LDLR*, *APOB* and *PCSK9* genes by the LIPOchip DNA array and copy number changes in the *LDLR* gene followed by sequencing of the *LDLR* gene for test-negatives on the chip. In the study by Alonso and colleagues,[39] LIPOchip detected mutations in the *LDLR* and *APOB* genes and also large rearrangements, followed by sequencing of the *LDLR* gene for test-negatives. Callaway and colleagues[40] reported the performance of LIPOchip against dHPLC/sequencing and MLPA in one of the genetic laboratories in the UK, in which all samples (negative on Elucigene FH20) received LIPOchip and also sequencing and MLPA, analysing all three genes. The study by Tejedor and colleagues[43] reported only the performance of the DNA array in detecting point mutations in the *LDLR* and *APOB* genes.

The studies by Palacios and colleagues[41] and Callaway and colleagues[40] reported detection of FH mutations in a UK population using version 8 of LIPOchip, which included 251 of the most prevalent mutations in Spain, the Netherlands, Italy and the UK. Information on version 10 of LIPOchip, which was developed by analysing 1000 patients from several cohorts, was obtained from the manufacturer based on the former study.[41] This version of the chip detects 189 of the most frequent FH mutations known to occur in the UK population and can also detect copy number changes in the *LDLR* gene. Palacios and colleagues[41] analysed samples from Newcastle and from Wales using version 8, and version 8 or version 9 of LIPOchip, respectively; however, the Welsh samples did not have information on clinical diagnosis (response by manufacturer to queries) and therefore did not meet the review's inclusion criteria.

Stef and colleagues[42] reported on a Spanish version of LIPOchip containing 247 of the most frequent Spanish FH mutations (238 *LDLR*, three *APOB* and six *PCSK9*) designed to detect point mutations in the *LDLR*, *APOB* and *PCSK9* genes and copy number changes in the *LDLR* gene. Alonso and colleagues[39] also evaluated the performance of a Spanish version of the LIPOchip platform containing a DNA array designed to detect 191 different point mutations in the *LDLR* gene and four different mutations in the *APOB* genes and adapted QMFSP for the analysis of large deletions or insertions in the *LDLR* gene. Tejedor and colleagues[43] reported the earliest version of LIPOchip comprising a DNA array including 118 mutations (117 *LDLR* and one *APOB*) as identified from SSCP/sequencing/restriction polymorphism analysis, with more than half of these mutations having been reported in Holland, France, Germany, Italy, Greece, the UK and the USA.

In all of these studies (except in the study by Callaway and colleagues[40]), the analysis was performed in the manufacturer's laboratory in Spain.

The study by Palacios and colleagues[41] was the only study that used DNA samples from patients with a clinical diagnosis based on the Simon Broome criteria. All of the samples had previously undergone genetic testing comprising Elucigene FH20 followed by, for test-negatives, SSCP/dHPLC/direct sequencing of all exons and finally MLPA for test-negatives on the previous test. In the study by Callaway and colleagues[40] selection criteria included one or more of the following: clinical diagnosis of Simon Broome 'definite FH' or high cholesterol (> 8 mmol/l) with family history of high cholesterol or cardiovascular disease. Alonso and colleagues[39] included unrelated cases with a clinical diagnosis of definite or probable FH based on the Dutch criteria (all participants had a score of ≥ 6 points). The studies by Stef and colleagues[42] and Tejedor and colleagues[43] included participants with a clinical diagnosis based on Dutch–MedPed criteria. Tejedor and colleagues[43] included patients with definite FH (score ≥ 8 points) and probable or possible FH (score 4–8 points).

Four studies reported the detection rate of FH by LIPOchip but only three[39,41,42] provided true-positive test data for each stage of testing and overall, to allow calculation of the sensitivity of LIPOchip in the diagnosis of FH against CGA. One study reported true-positive, true-negative, false-positive and false-negative data along with sensitivity and specificity.[40] The studies by Alonso and colleagues[39] and Tejedor and colleagues[43] reported the diagnostic accuracy (sensitivity and specificity) of the LIPOchip DNA array at the mutational level. The sensitivity of the array was determined by the number of mutations detected by sequencing *LDLR* in the samples in which the DNA array failed to detect mutations, whereas specificity was determined by random verification of DNA array-positive samples by automatic sequencing.

The studies by Palacios and colleagues[41] and Alonso and colleagues[39] provided information on the time taken to obtain LIPOchip platform results.

None of the LIPOchip studies reported results for cascade testing of relatives.

Low-density lipoprotein cholesterol as part of the Simon Broome criteria

The studies by Civeira and colleagues,[44] Damgaard and colleagues,[45] Mabuchi and colleagues[46] and Widhalm and colleagues[47] reported the diagnostic accuracy of LDL-C using the Simon Broome criteria cut-offs against a reference standard of genetic analysis. However, only the study by Civeira and colleagues[44] reported the analysis of all three genes (*LDLR*, *APOB*, *PCSK9*), using the LIPOchip platform designed to detect 203 mutations. Two studies analysed *LDLR* and *APOB* genes by using screening of three common mutations in a Danish population/SSCP/sequencing/*APOB* analysis/MLPA[45] or PCR/DGGE/sequencing,[47] whereas the study by Mabuchi and colleagues[46] reported an analysis of the *LDLR* gene only, by using PCR/DGGE/direct sequencing/Southern blot analysis.

TABLE 8 Summary of the characteristics of studies reporting LDL-C

Study, country	Study design, total sample (*n*)	Study population	Methods (number evaluated for each test)	Genes tested	Setting, (prevalence of FH[a])
Civeira 2008[44] Spain	Cross-sectional comparative (consecutive), 825 (index cases)	Clinically diagnosed patients (≥14 years) who underwent genetic testing were retrospectively categorised based on Simon Broome, Dutch or MedPed criteria (definite, possible or probable FH) Adults and adolescents	Test 1 (825): LIPOchip platform (203 mutations) (DNA array/QMFSP/sequencing) Test 2 (825): LDL-C test as part of Simon Broome, Dutch, MedPed criteria	*LDLR*, *APOB*, *PCSK9*	Three lipid clinics, one genetics laboratory in Spain (55.6%)
Damgaard 2005[45] Denmark	Cross-sectional comparative, 408 (index cases), 385 (relatives)	Clinically diagnosed patients categorised based on Simon Broome, Dutch or MedPed criteria before genetic analysis (definite, possible or probable FH) Adults	Test 1 (408*):* LDL-C test as part of Simon Broome, Dutch, MedPed criteria Test 2 (408): CGA (screening of three common mutations in Danish population/SSCP/sequencing/*APOB* analysis/MLPA) Test 3 (385): targeted sequencing of relatives	*LDLR*, *APOB*	One lipid clinic, genetics laboratory in Denmark (33.1%)
Lee 2010[48] UK	Cross-sectional comparative, 30 (index cases, all homozygous), 90 (relatives, all heterozygotes)	Clinically diagnosed index cases based on Simon Broome criteria and genetic test and their relatives	Test 1 (90): CGA (Elucigene FH20/dHPLC/MLPA or LIPOchip/sequencing or iPLEX/sequencing/MLPA) Test 2 (90): age- and gender-specific LDL-C cut-offs (NICE guideline[1])	*LDLR*, *APOB*, *PCSK9*	Three (two UK, one Spain) genetics laboratories (not calculable)
Mabuchi 2005[46] Japan	Cross-sectional comparative, 281 (index cases)	Clinically diagnosed index cases based on TC ≥ 5.9 mmol/l and < 12.9 mmol/l) with tendon xanthomata or primary hypercholesterolaemia with/without tendon xanthomata in a family with FH patients among first-degree relatives (Yu 2002[51]) and genetic test (*LDLR* gene mutation) and unaffected first- and second-degree relatives Adults	Test 1 (281): CGA (PCR/DGGE/direct sequencing of *LDLR* gene/Southern blot analysis) Test 2 (281): LDL-C cut-offs > 4.0 mmol/l	*LDLR*	(Probably) Japan (64.4%)

Study, country	Study design, total sample (*n*)	Study population	Methods (number evaluated for each test)	Genes tested	Setting, (prevalence of FH[a])
Starr 2008[49] UK	Cross-sectional comparative, all relatives, the Netherlands = 3294, Denmark = 321, Norway = 1116	Clinically diagnosed index cases based on Dutch criteria (the Netherlands), a combination of lipid levels, clinical characteristics and family history (Norway and Denmark) and genetically tested cohort of first-degree relatives from three European countries Adults, adolescents and children	Test 1: CGA (DGGE/direct sequencing/PCR or screening of three common mutations in Danish population/SSCP/ sequencing/MLPA or sequencing/MLPA) Test 2: age- and gender-specific LDL-C cut-offs (NICE guideline[1]) Test 3: MedPed age-specific LDL-C cut-offs (the Netherlands = 3294, Denmark = 321, Norway = 1116; all received tests 1, 2 and 3)	*LDLR*, *APOB*	Laboratories in the Netherlands, Denmark and Norway (the Netherlands = 25.1%, Denmark = 9.8%, Norway = 34.0%)
Wiegman 2003[50] The Netherlands	Cross-sectional comparative, 591 (index cases), 1034 (first-degree relatives – children)	Children of index parents with definite FH (*LDLR* gene mutation or clinical diagnosis)	Test 1 (1034): CGA (PCR/DGGE/sequencing/Southern blot) Test 2 (282): age- and gender-specific LDL-C (≥ 3.50 mmol/l) cut-offs for those whose genetic test not yet established	*LDLR*	Lipid clinics in the Netherlands (76.6%)
Widhalm 2007[47] Austria	Cross-sectional comparative, 263 (index cases – adults = 147, children = 116)	Clinically diagnosed based on MedPed (definite or possible FH) Adults and children	Test 1 (119): LDL-C > 5.1 mmol/l in index cases, LDL-C > 4.0 mmol/l in relatives Test 2 (263): CGA (PCR/DGGE/sequencing)	*LDLR*, *APOB*	Tests were performed in Vienna (45.3%; adults 42.2%, children 49.1%)

iPLEX, multiple MassARRAY spectometry.

a Prevalence of FH represents the total FH diagnosed with genetic testing as a percentage of the total number of study population in that setting.

The study by Damgaard and colleagues[45] also reported cascade testing by targeted sequencing of relatives.

Age-and gender-specific low-density lipoprotein cholesterol cut-offs according to the NICE clinical guideline

The studies by Lee and colleagues,[48] Starr and colleagues[49] and Wiegman and colleagues[50] reported the test performance of age- and gender-specific LDL-C cut-offs according to the NICE clinical guideline CG71[1] against a reference standard of CGA, in cascade testing of relatives for the diagnosis of FH.

Lee and colleagues[48] evaluated the validity of these cut-offs in a Welsh population and compared them with genetic testing. This study included index cases with a definite diagnosis of homozygous FH based on the Simon Broome criteria and genetic testing from an ongoing national cascade testing project in Wales, and genetically tested relatives of genotyped FH index cases. Genetic tests were performed in three different laboratories (two in the UK and one in Spain), which included screening the *LDLR*, *APOB* and *PCSK9* genes using Elucigene FH20/ dHPLC/MLPA or LIPOchip/sequencing or multiple MassARRAY spectrometry (iPLEX) (50 mutations)/sequencing/MLPA.

In the study by Starr and colleagues,[49] age- and gender-specific LDL-C cut-offs were derived from a genetically tested large Dutch cohort of relatives with known mutational status and validated against genetically tested cohorts from Denmark and Norway in which the participants were first-degree relatives of index cases with a definite genotyped diagnosis of FH, and also compared with the MedPed age-specific LDL-C cut-offs. Genetic testing of cohorts was performed in three different countries (the Netherlands, Norway and Denmark) and included analysis of the *LDLR* and *APOB* genes using (1) screening for three common mutations in the Danish cohort using SSCP/sequencing/MLPA or (2) sequencing of all exons/MLPA in the Norwegian cohort or (3) PCR/DGGE/direct sequencing in the Dutch cohort.

In the study by Wiegman and colleagues,[50] age-specific LDL-C cut-offs ≥ 3.50 mmol/l were derived from children who had been genetically tested (PCR/DGGE/sequencing/Southern blot of the *LDLR* and *APOB* genes) and who came from families with a definite diagnosis of FH based on either (1) a documented LDL mutation or (2) plasma LDL-C levels above the 95th percentile for age and gender in a family with a history of premature cardiovascular disease (PCVD) along with (3) tendon xanthomata. The LDL-C cut-offs used in this study represented the red zone of the age- and gender-specific criteria as recommended by the NICE guideline, in which children are likely to have a clinical diagnosis of FH.

Quality of the included studies

Figures 4, *5* and *6* summarise the results of the quality assessment of the full-text studies reporting Elucigene FH20 (one study), LIPOchip (two studies) and LDL-C (six studies) respectively. Quality assessment results for the individual studies (nine full text) are summarised in *Appendix 9*. For the purposes of the quality assessment, Elucigene FH20, LIPOchip and LDL-C were considered to be index tests and CGA the reference standard. Three questions were considered to be not applicable to studies reporting Elucigene FH20 or LIPOchip:

- Q8: 'Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?' This question was considered not applicable because this information would have no effect on the results of the tests.
- Q11: 'Were cut-off values established before the study was started?' This question was considered not applicable as there is no range of cut-off values applied, but rather a mutation is either detected or not.

- Q13: 'Did the study provide a clear definition of what was considered to be a "positive" result?' This question was considered to be not applicable as, similar to above, a mutation is either detected or not.

In the study by Taylor and colleagues[37] reporting Elucigene FH20, both studies reporting LIPOchip and 83% ($n = 5$) of the studies reporting LDL-C, the spectrum of patients was considered to be representative of those who would receive the test in practice. For this question patients were considered to be representative if they had received a clinical diagnosis of FH (index cases) or were relatives of index cases with confirmed FH. In the Elucigene FH20 study, one of the two LIPOchip studies and 50% ($n = 3$) of the LDL-C studies the reference standard used was considered likely to correctly classify FH. Given that the FH-causing *PCSK9* gene is rare and was discovered only fairly recently, for this question those studies that included DNA sequence analysis of the promoter, all exons, the exon/intron boundaries and into the 3′ untranslated region of the *LDLR* gene; MLPA for each exon and the promoter region of the *LDLR* gene to detect deletions and duplications; and *APOB* p.Arg3527Gln gene mutation analysis but without assessing the *PCSK9* p.Asp374Tyr gene mutation were still considered to be comprehensive and were considered to correctly classify FH in this assessment. The studies that were considered not to classify FH correctly either were missing a test for deletions and duplications in the *LDLR* gene (one LIPOchip study,[43] one LDL-C study[47]) or did not undertake *APOB* p.Arg3527Gln gene mutation analysis (two LDL-C studies[46,50]).

Partial verification bias was avoided in all LDL-C studies in that all patients who underwent LDL-C also received a reference standard, which was not the case with Elucigene FH20 or LIPOchip, for which only test-negatives went on to receive further genetic tests. In practical terms this meant that it was not possible to calculate the specificity of these studies, other than making an assumption of no false-positives and therefore 100% specificity. Differential verification bias was avoided (patients received the same reference standard test regardless of the index test results) in 83% ($n = 5$) of the LDL-C studies but none of the Elucigene FH20 or LIPOchip studies. In all nine studies incorporation bias was avoided in that the index test was considered to be independent of the reference standard test, even though, for Elucigene FH20 and LIPOchip, these tests formed part of a sequence of tests.

Test review bias was avoided (the results of the index test were interpreted without knowledge of the results of the reference standard) in the study reporting Elucigene FH20, one of the two studies reporting LIPOchip but only 33% ($n = 2$) of the LDL-C studies. It was unclear in the Elucigene FH20 study, both LIPOchip studies and 83% ($n = 5$) of the LDL-C studies whether or not diagnostic review bias had been avoided (the results of the reference standard being interpreted without knowledge of the results of the index test).

Clinical review bias was avoided (the same clinical data were available when the index test result were interpreted as would be available when the test was used in practice) in all of the LDL-C studies. In the Elucigene FH20 study, both LIPOchip studies and 83% ($n = 5$) of the LDL-C studies either un-interpretable test results were not reported or there were none, whereas in all nine studies either an explanation was not given for any withdrawals from the study or there were none. In three LDL-C studies (50%) cut-off values were established before the start of the study. The technology of the index test remained unchanged for Elucigene FH20 as this study reported the FH20 kit; however, the two LIPOchip studies reported earlier versions of this technology. Finally, in 50% ($n = 3$) of the LDL-C studies a clear definition of a positive result was given.

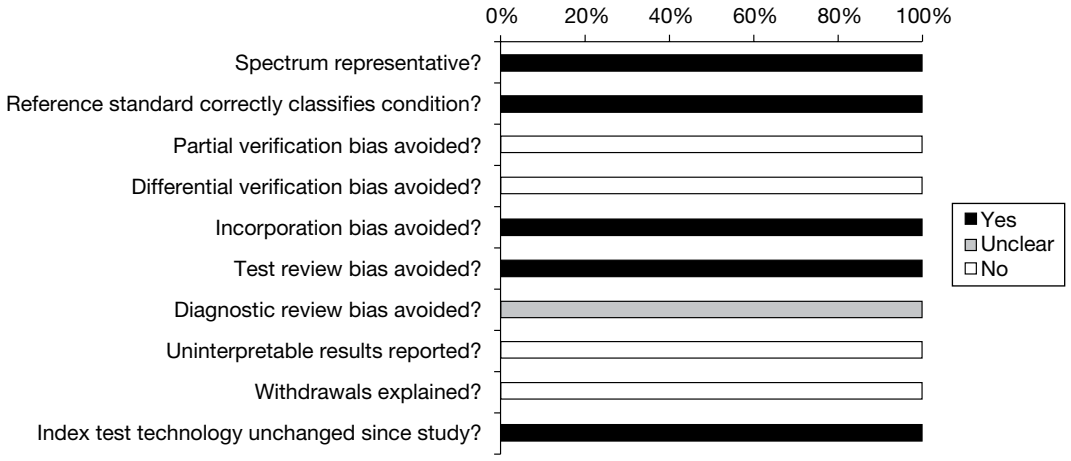

FIGURE 4 Summary of quality assessment of Elucigene FH20 studies ($n = 1$).

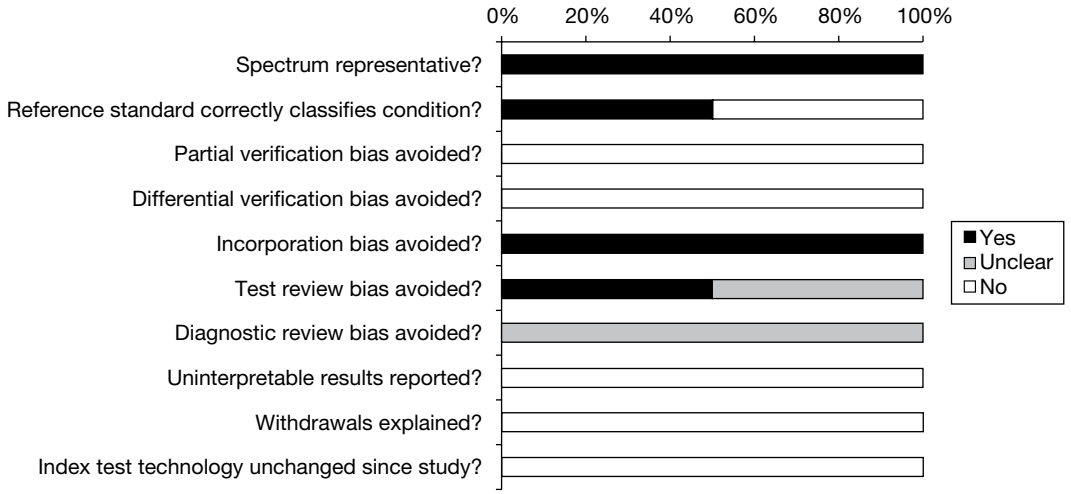

FIGURE 5 Summary of quality assessment of LIPOchip studies ($n = 2$).

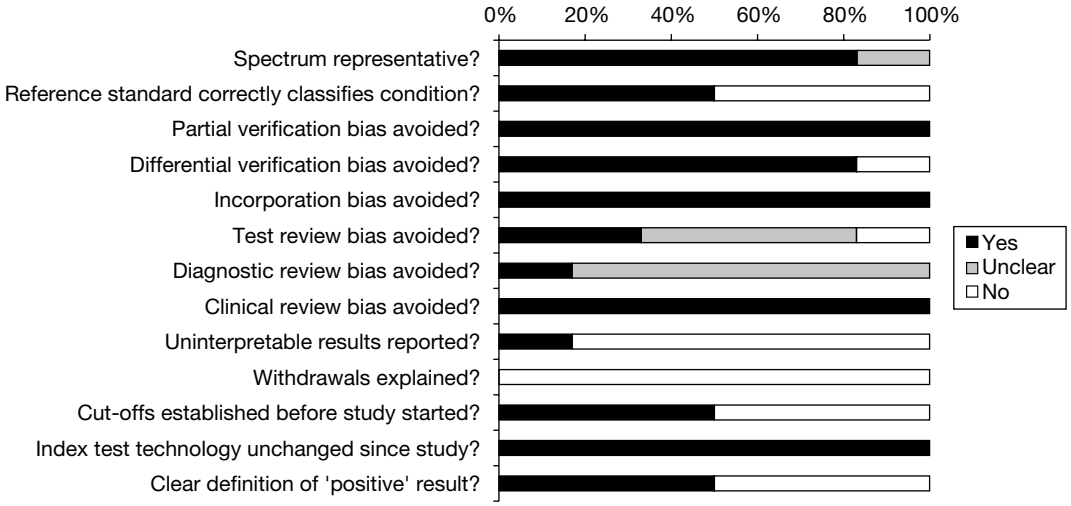

FIGURE 6 Summary of quality assessment of LDL-C studies ($n = 6$).

Assessment of test performance

Overview

This section reports the performance of the index tests Elucigene FH20 and LIPOchip and comparator test LDL-C against a reference standard in the diagnosis of FH in index cases and for cascade testing of relatives. Elucigene FH20 and LIPOchip are designed to detect mutations that are most frequent in the European Caucasian population and which have already been identified using sequencing techniques, a 'gold standard' of genetic tests, in this population. Therefore, the mutational analysis of these techniques against the gold standard is most likely to give 100% sensitivity and 100% specificity in this population. Therefore, the results focus mainly on patient-level analysis at trial level. Studies evaluating Elucigene FH20 or LIPOchip comprised a sequence of genetic tests in which the participants received the index test as a pre-screen and test-negatives would then receive further genetic tests such as gene sequencing and MLPA. None of the studies directly compared Elucigene FH20 or LIPOchip with LDL-C, and none reported the acceptability or interpretability of the test or the clinical effectiveness outcomes resulting from use of the test. The results for each of the different tests are reported under the broad headings of *Diagnosis of index cases* and *Cascade testing of relatives*. This is followed by sections on other outcomes and subgroup analysis, including by ethnicity, region and type of gene, followed by a brief summary of the chapter. Individual study results are given in *Appendix 10*.

Diagnosis of index cases

Elucigene FH20

Table 9 shows the test performance results for the three studies that reported Elucigene FH20, by Taylor and colleagues,[37] Hooper and colleagues[36] and Yarram,[38] involving 802 participants. Taylor and colleagues[37] and Yarram[38] reported the performance of Elucigene FH20 in detecting FH-causing mutations in patients with a clinical diagnosis of definite FH and possible FH and overall for both (Simon Broome criteria) against CGA, whereas Hooper and colleagues[36] reported the performance of Elucigene FH20 for those with a clinical diagnosis of definite FH (Dutch criteria) against CGA. Sensitivity of Elucigene FH20 in detecting FH-causing mutations in overall clinical diagnosis ranged from 44.0% in the study by Taylor and colleagues[37] to 52.0% in the study by Yarram.[38] Data were not pooled because there was no information on true- and false-positives and negatives in the study by Yarram[38] to compute a CI.

Taylor and colleagues[37] reported sensitivities of 48.6% and 40.2% of Elucigene FH20 in detecting FH in patients with a clinical diagnosis of 'definite' and 'possible' FH respectively. Hooper and colleagues[36] reported a lower sensitivity of Elucigene FH20 of 28.6% in detecting FH in those with a clinical diagnosis of definite FH. The difference may be explained at least in part by the fact that the two studies used different clinical diagnostic criteria and that the Elucigene FH20 kit was used in two different populations (UK and Australia), given that the kit is designed to screen for the most common mutations in the UK population. For the same reason, a pooled estimate was not calculated but the estimated sensitivities of Elucigene FH20 in confirming FH-causing mutations of definite FH are represented graphically to visualise the heterogeneity (*Figure 7*). The specificity of Elucigene FH20 in these studies could not be calculated as test-positives did not go on to receive a reference standard test.

A previous report[54] to Taylor and colleagues[37] provided information on an earlier version of Elucigene (FH13). In this report the FH13 kit was validated against a reference standard of sequencing the *LDLR* gene in a patient population in which all patients were clinically diagnosed with definite or possible FH based on the Simon Broome criteria and all received testing with the kit and sequencing of the *LDLR* gene. The sensitivity of the kit was found to be 30% for patients with a clinical diagnosis of possible FH, 52% for patients with definite FH and 38% for those with a clinical diagnosis of definite or possible FH (*Table 10*).

TABLE 9 Sensitivity: individual study results for Elucigene FH20

Study, country	Diagnosis	Criteria	*n*	Sensitivity (%)
Hooper 2009[36] Australia	DFH	Dutch	63	28.6
Taylor 2010[37a] England	DFH	Simon Broome	190	48.6
Taylor 2010[37a] England	PFH	Simon Broome	394	40.2
Taylor 2010[37a] England	UFH	Simon Broome	51	38.5
Taylor 2010[37a] England	DFH/PFH/UFH	Simon Broome	635	44.0
Yarram 2010[38] England	DFH/PFH/UFH	Simon Broome	104	52.0

DFH, definite FH; PFH, possible FH; UFH, unclassified FH.
a In Taylor 2010 initial testing was carried out with the FH13 kit and then later the FH20 kit was used, but detection rate data were reported as if all samples were tested using FH20.
Reference standard: Elucigene FH20 + MLPA for test-negative with Elucigene + sequencing for test-negative with MLPA (included *LDLR*, *PCSK9*, *APOB* genes).

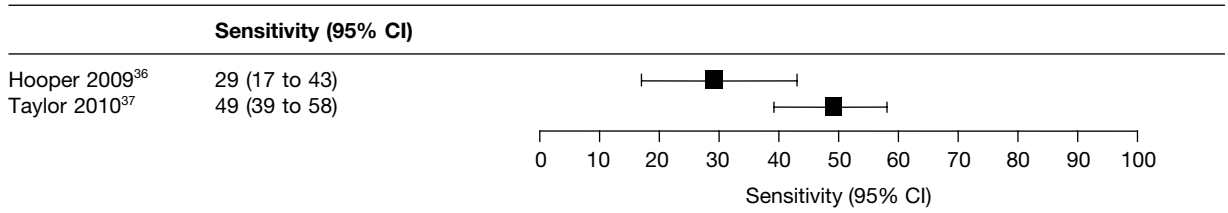

FIGURE 7 Forest plot of Elucigene FH20 sensitivity for patients with a clinical diagnosis of definite FH.

TABLE 10 Sensitivity: individual study results for Elucigene FH13

Study	Diagnosis	Test(s) evaluated	*n*	Sensitivity (%)
Taylor 2007[54] (linked to Taylor 2010[37])	DFH	Elucigene FH13	400	52
	PFH	Elucigene FH13	400	30
	DFH/PFH	Elucigene FH13	400	38
	DFH/PFH	SSCP/dHPLC (*LDLR* only)	400	62

DFH, definite FH; PFH, possible FH.
Reference standard: Elucigene FH13 + SSCP/dHPLC (included *LDLR*, *PCSK9*, *APOB* genes but no MLPA).

Mutation-level analysis The previous report[54] to the study by Taylor and colleagues[37] reported that there were no false-positive and no false-negative results from the Elucigene FH13 kit for detection of FH-causing mutations in patients.

In the study by Taylor and colleagues,[37] 99 mutations plus eight different deletions and duplications were identified in total. Of the 20 mutations present in the Elucigene FH20 kit, three were not identified in any of the participants. Taylor and colleagues[37] also reported the prevalence

of each mutation that was present in the Elucigene FH20 kit and was identified in the study. The most frequently identified mutations were the mutation in the *APOB* gene, with a prevalence of 12%, and the three *LDLR* mutations, p.Gly218del, the intron 3 splice variant c.313+1G>A and the *p*.Pro685Leu exon 14 variant, with a prevalence of 5% of the total mutations detected.

LIPOchip

Table 11 shows the test performance results for the four studies that reported LIPOchip, by Alonso and colleagues,[39] Callaway and colleagues,[40] Palacios and colleagues[41] and Stef and colleagues,[42] and involving 3418 participants. The studies used different versions of LIPOchip. Palacios and colleagues[41] and Callaway and colleagues[40] reported results for LIPOchip version 8 (Spanish version but study conducted in the UK). Based on the sample reported in Palacios and colleagues,[41] the manufacturer of LIPOchip provided further information on version 10, which contains mutations specific to the UK population. Alonso and colleagues[39] and Stef and colleagues[42] used Spanish versions but did not provide information on the version number. Although the Spanish versions are not specific to the UK, they cover the mutations that are more frequent in Western Europe including the UK.

The sensitivity reported by the studies ranged from 33.3%[40] (LIPOchip version 8, Simon Broome criteria) to 94.5%[42] (Spanish version designed to detect 247 mutations, Dutch–MedPed criteria). Palacios and colleagues[41] reported sensitivity of 56.9% for LIPOchip version 8, which was based on 126 samples (120 analysed). Based on the above sample, the sensitivity of LIPOchip UK version 10 would be 78.5% (51/65) (Progenika, 2011, personal communication) There was heterogeneity across the studies, particularly in relation to Palacios 2010[41] (version 8 LIPOchip) and Stef 2009,[42] and therefore a pooled estimate was not calculated. The estimated sensitivities (with 95% CIs) of LIPOchip in confirming FH-causing mutations are graphically represented to visualise the heterogeneity (*Figure 8*). The heterogeneity may be explained at least in part by the fact that different versions of LIPOchip and different clinical diagnostic criteria were used. In addition, the difference may also be explained by the fact that the LIPOchip kit was used in two different populations (UK and Spain), given that the prevalence of the FH-causing mutations varies according to the country of origin. The specificity of FH detection by LIPOchip in three studies could not be calculated as test-positives did not go on to receive a reference standard test.[39,41,42] In the study by Callaway and colleagues[40] the specificity of LIPOchip version 8 was reported to be 93.8% with one false-positive diagnosis.

None of the included LIPOchip studies reported accuracy data according to definite or possible FH.

Mutation-level analysis In a mutational-level analysis, the studies by Alonso and colleagues,[39] Palacios and colleagues[41] and Tejedor and colleagues[43] reported sensitivity and specificity of LIPOchip of around 100%. Results on validation with mutation-negative samples and LIPOchip-positive samples by sequencing and QMFSP against MLPA were reported in these studies. See *Appendix 10* for the tabulated results.

In the study by Tejedor and colleagues,[43] 59/118 mutations were detected using this earliest version of LIPOchip. Palacios and colleagues[41] reported that in 37 patients 17/251 mutations were picked up by LIPOchip and in 28 patients 25/251 mutations were picked up by sequencing. Overall, the mutation detection rate (by the LIPOchip platform) was 42/251 mutations in 65 patients.[41]

Low-density lipoprotein cholesterol

Table 12 shows the test performance results for the four studies that reported LDL-C, by Civeira and colleagues,[44] Damgaard and colleagues,[45] Mabuchi and colleagues,[46] and Widhalm and

TABLE 11 Sensitivity: individual study results for LIPOchip

Study, country	LIPOchip version	Diagnosis	Criteria	*n*	Sensitivity (%)	Specificity (%)
Palacios 2010[41] and data received from the manufacturer UK	Version 10, UK mutations	NR	Simon Broome	126	78.5	NC
Callaway 2010[40] UK	Version 8 (251 mutations)	DFH or possible FH	Simon Broome	22	33.3	93.8
Palacios 2010[41] UK	Version 8 (251 mutations)	NR	Simon Broome	120	56.9	NC
Stef 2009[42] Spain	247 mutations	NR	Dutch–MedPed	2462	94.5	NC
Alonso 2009[39] Spain	195 mutations	DFH or probable FH	Dutch criteria	808	78.0	NC

DFH, definite FH; NC, not calculable (test-positives on LIPOchip did not receive a reference standard test); NR, not reported.
Reference standard: (1) LIPOchip platform (DNA array + QMFSP for test-negative + sequencing for test-negative) (*LDLR*, *APOB*) (Alonso 2009[39]); (2) LIPOchip platform (LIPOchip including copy number changes in the *LDLR* gene + sequencing of the *LDLR* gene for test-negatives on the chip) (*LDLR*, *PCSK9*, *APOB*) (Palacios 2010,[41] Stef 2009[52]); (3) Elucigene FH20 + dHPLC/sequencing + MLPA (*LDLR*, *PCSK9*, *APOB*) (Callaway 2010[40]). Elucigene FH20 + SSCP/dHPLC/direct sequencing + MLPA against reference standard 2, sensitivity = 95% (*n* = 126).

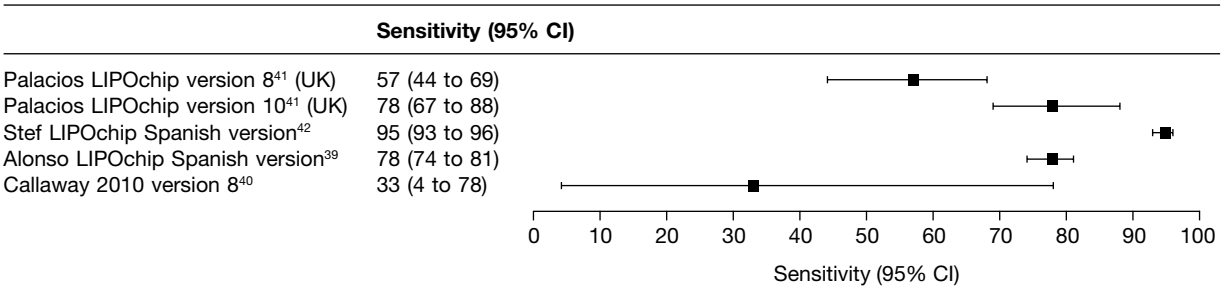

FIGURE 8 Forest plot of LIPOchip sensitivity for patients with a clinical diagnosis of FH.

colleagues,[47] involving 1777 participants. The sensitivity of LDL-C as part of the Simon Broome criteria for those with a clinical diagnosis of possible or definite FH was 90%[45] and 93%,[44] although specificity was much lower at 29% and 28% respectively. The sensitivity of LDL-C as part of the Dutch criteria was 88%[44] and 99%,[45] although specificity again was also much lower at 18% and 6% respectively. For LDL-C as part of the MedPed criteria the sensitivity reported was 54%[45] and 91%,[44] although specificity was 83% and 53% respectively. Widhalm and colleagues[47] reported sensitivity of LDL-C as part of the MedPed criteria separately for adults and children (66% and 81% respectively), whereas Mabuchi and colleagues[46] in a study from Japan reported sensitivity of 98% for LDL-C at a cut-off of > 4 mmol/l. We could not reproduce the specificity of 98.5%, as was reported in this study, from the given values.

Cascade testing of relatives

Age- and gender-specific low-density lipoprotein cholesterol cut-offs

Table 13 shows the results for the three studies that used LDL-C age- and gender-specific cut-offs as recommended in NICE clinical guideline CG71[1] for cascade testing of relatives of index cases with FH.

TABLE 12 Sensitivity and specificity: individual study results for LDL-C for index cases

Study	Criteria	Diagnosis	*n*	Sensitivity (%)	Specificity (%)	LR+	LR–	Reference standard: CGA
Damgaard 2005[45]	Simon Broome	Overall	408	90	29	1.3	0.3	Screening of three common mutation in Danish population/ SSCP/sequencing/MLPA (*LDLR*, *APOB*)
	Dutch		408	99	6	1.1	0.1	
	MedPed		408	54	83	3.1	0.6	
Civeira 2008[44]	Simon Broome	Overall	825	93	28	1.3	0.3	DNA array/QMFSP/sequencing (*LDLR*, *APOB*, *PCSK9*)
		DFH		59	93	8.4	0.4	
		PFH		90	27	1.2	0.4	
	Dutch	Overall	825	88	18	1.1	0.7	
		DFH		72	83	4.2	0.3	
	MedPed	Overall	825	91	53	1.9	0.2	
Widhalm 2003[47]	MedPed	Adults	147	66	NC	0.7	NC	PCR/DGGE/sequencing (*LDLR*, *APOB*); no test for deletion and duplication
		Children	116	81	NC	0.8	NC	
Mabuchi 2005[46]	LDLC > 4 mmol/l[a]		281	98	NC[b]	NC	0.0	PCR/DGGE/sequencing/Southern blot analysis (*LDLR*)

DFH, definite FH; LR+, positive likelihood ratio; LR–, negative likelihood ratio; NC, not calculable; PFH, possible FH.

a Mabuchi and colleagues reported performance of LDL-C > 4 mmol/l with other clinical criteria being sufficiently similar to Simon Broome criteria.

b Specificity of 98.5% reported in the study but was not reproducible from the given values.

TABLE 13 Sensitivity and specificity: age- and gender-specific LDL-C cut-offs for cascade testing

Study	Country	Participants	*n*	Sensitivity (%)	Specificity (%)	Reference standard: CGA
Lee 2010[48]	UK	Relatives	90	91.5	93.0	Elucigene/dHPLC/MLPA or LIPOchip/ sequencing or iPLEX/sequencing/ MLPA (*LDLR*, *APOB*, *PCSK9*)
		45–54 years		80.0	70.0	
Starr 2008[49]	The Netherlands	First-degree relatives	3294	68.0	85.2	DGGE/sequencing/PCR (*LDLR*, *APOB*)
	Denmark	First-degree relatives	321	79.4	85.1	Screening of three common mutations in Danish population/ SSCP/sequencing/MLPA (*LDLR*, *APOB*)
	Norway	First-degree relatives	1116	83.7	83.8	Sequencing/MLPA (*LDLR*)
Wiegman 2003[50]	The Netherlands	Children of definite FH parents	611	96.0	NC	PCR/DGGE/sequencing/Southern blot (*LDLR*)

NC, not calculable.

Lee and colleagues[48] reported sensitivity and specificity of 91.5% and 93%, respectively, in the UK cohort.

Wiegman and colleagues[50] reported 96% sensitivity for those with LDL-C cut-offs ≥ 3.50 mmol/l (age adjusted), which represents the LDL-C cut-off value in children as stated in NICE clinical guideline CG71.[1] Because of the lack of information on false-positive diagnosis, specificity could not be calculated for this LDL-C cut off. All of the parents of these children had a definite diagnosis of FH. Wiegman and colleagues[50] further reported that, out of 228 children of genetically or clinically diagnosed FH parents, 131 (57%) had LDLC ≥ 3.50 mmol/l.

Starr and colleagues,[49] for the first-degree relatives, reported sensitivity of 68.0% (the Netherlands), 79.4% (Denmark) and 83.7% (Norway), with specificity of around 85% for all three groups. Starr and colleagues[49] also reported test performance by age band including 0–14 years, 15–24 years, 35–44 years, 45–54 years and ≥ 55 years (*Table 14*). In the Netherlands ($n = 3294$) and Norway ($n = 1116$) cohorts, the test performance of LDL-C decreased as the age increased, with a sensitivity ranging from 84.7% (specificity 93.4%) in the < 15 years group to 38.2% (specificity 85.6%) in the 55+ years group (the Netherlands cohort) and sensitivity of 92.5% (specificity 93.5%) in the < 15 years group to 66.7% (specificity 79%) in the 55+ years group (Norway cohort). In the Danish cohort ($n = 321$) the sensitivity increased as age increased with 95.5% sensitivity in the older group (55+ years) and 76.2% sensitivity in the younger group (15–24 years). Test specificity in this cohort varied across groups, at 72.4% in the 45–54 years group to 94.4% in the 25–34 years group. Starr and colleagues also reported the performance of MedPed LDL-C cut-offs in these cohorts, reporting low sensitivity but consistently higher specificity compared with the age- and gender-specific LDL-C cut-offs.

Targeted gene sequencing for a mutation found in a family member

Table 15 shows the results of the four studies that investigated cascade testing of relatives. Three studies reported cascade testing of relatives using targeted gene sequencing for a mutation in a family member.[37,45,50] One study published as a presentation did not specify whether or not cascade testing was carried out by targeted sequencing.[38] Three of these studies reported that 53–56% of relatives were positive for FH,[37,38,45] which was more or less consistent with the expected 50% probability of diagnosis in relatives.

TABLE 14 Sensitivity and specificity: age-and gender-specific LDL-C cut-offs in first-degree relatives by age group

	n	+ve/–ve mutation	Sensitivity (95% CI) (%)	Specificity (95% CI) (%)	False-negative (95% CI) (%)	False-positive (95% CI) (%)
The Netherlands						
0–14 years		183/243	84.7 (78.7 to 89.6)	93.4 (89.5 to 96.2)	15.3 (10.4 to 21.3)	6.6 (3.8 to 10.5)
15–24 years		187/276	71.1 (64.1 to 77.5)	85.1 (80.4 to 89.1)	28.9 (22.5 to 35.9)	14.9 (10.9 to 19.6)
25–34 years		138/293	64.5 (55.9 to 72.4)	82.6 (77.8 to 86.8)	35.5 (27.6 to 44.1)	17.4 (13.2 to 22.2)
35–44 years		136/471	71.3 (62.9 to 78.7)	83.4 (79.8 to 86.7)	28.7 (21.3 to 37.1)	16.6 (13.3 to 20.2)
45–54 years		92/449	57.6 (46.9 to 67.9)	83.7 (80.0 to 87.0)	42.4 (32.1 to 53.1)	16.3 (13.0 to 20.0)
55+ years		89/737	38.2 (28.1 to 49.1)	85.6 (82.9 to 88.1)	61.8 (50.9 to 71.9)	14.4 (11.9 to 17.1)
Overall	3294	825/2469	68.0 (64.7 to 71.2)	85.2 (83.8 to 86.6)	32 (28.3 to 35.3)	14.8 (13.4 to 16.2)
Denmark[a]						
15–24 years		42/23	76.2 (60.5 to 87.9)	91.3 (72.0 to 98.9)	23.8 (12.1 to 39.5)	8.7 (1.1 to 28)
25–34 years		34/36	58.8 (40.7 to 75.4)	94.4 (81.3 to 99.3)	41.2 (24.6 to 59.3)	5.6 (0.7 to 18.7)
35–44 years		39/27	89.7 (75.8 to 97.1)	81.5 (61.9 to 93.7)	10.3 (2.9 to 24.2)	18.5 (6.3 to 38.1)
45–54 years		18/29	88.9 (65.3 to 98.6)	72.4 (52.8 to 87.3)	11.1 (1.4 to 34.7)	27.6 (12.7 to 47.2)
55+ years		22/40	95.5 (77.2 to 99.9)	90.0 (76.3 to 97.2)	4.6 (0.1 to 22.8)	10.0 (2.8 to 23.7)
Overall	321	160 /161	79.4 (72.3 to 85.4)	85.1 (78.6 to 90.2)	20.6 (14.6 to 27.7)	14.9 (9.8 to 21.4)
Norway						
0–14 years		106/107	92.5 (85.7 to 96.7)	93.5 (87.0 to 97.3)	7.6 (3.3 to 14.3)	6.5 (2.7 to 13.0)
15–24 years		82/103	86.6 (77.3 to 93.1)	91.3 (84.1 to 95.9)	13.4 (6.9 to 22.7)	8.7 (4.1 to 15.9)
25–34 years		69/124	87.0 (76.7 to 93.9)	85.5 (78.0 to 91.2)	13.0 (6.1 to 23.3)	14.5 (8.8 to 22.0)
35–44 years		51/145	78.4 (64.7 to 88.7)	82.8 (75.6 to 88.5)	21.6 (11.3 to 35.3)	17.2 (11.5 to 24.4)
45–54 years		39/120	66.7 (49.8 to 80.9)	74.2 (65.4 to 81.7)	33.3 (19.1 to 50.2)	25.8 (18.3 to 34.6)
55+ years		27/143	66.7 (46.0 to 83.5)	79.0 (71.4 to 85.4)	33.3 (16.5 to 54.0)	21.0 (14.6 to 28.6)
Overall	1116	374/742	83.7 (79.5 to 87.3)	83.8 (81.0 to 86.4)	16.3 (12.7 to 20.5)	16.2 (13.6 to 19.0)
MedPed age-specific LDL-C cut-offs						
The Netherlands[b]	3294		42.3	97.8	57.7	2.2
Denmark	321		68.8	89.4	31.3	10.6
Norway[b]	1116		74.9	92.7	25.1	7.3

a Please note that all the figures presented in this table were sourced from Starr and colleagues,[49] where an error was observed in the total number reported for Denmark group (the age subgroups do not add to the total reported). Authors were unable to get the correct values from the original source.

b Significant compared with age- and gender-specific LDL-C cut-offs of this study.

Source of data: Starr and colleagues.[49]

Taylor and colleagues[37] reported results of cascade testing of relatives of index cases with a documented mutation who had received an initial clinical diagnosis based on the Simon Broome criteria. This study used a sequence of tests for detecting mutations in index cases that included Elucigene FH20 as a pre-screen test and then sequencing for test-negatives on Elucigene FH20, which in turn was followed by MLPA for test-negatives on sequencing. Relatives of the index cases received targeted gene sequencing for the specific mutation found in the family member. A total of 296 first-degree relatives from 100 families were recruited and a FH-causing mutation was identified in 56%. The detection rate was similar (around 55%) in relatives from families with an initial diagnosis of definite FH or an initial diagnosis of possible FH. Yarram[38] used a similar approach as in the study by Taylor and colleagues[37] to diagnose index cases and reported

TABLE 15 Proportion of FH identified through cascade testing using targeted sequencing

Study	Country	Study participants	Test	Number of index cases/ families	Number of relatives tested	Number identified with FH (%)
Damgaard 2005[45]	Denmark	Relatives of index cases in whom a mutation was identified	Index cases: screening of initial three common mutations + SSCP + sequencing + *APOB* analysis + MLPA (*LDLR*/*APOB*)	408	385	205 (53)
			Relatives: targeted sequencing in relatives			
Taylor 2010[37]	UK	First-degree relatives of index cases in whom a mutation was identified	Index cases: Elucigene FH20 + SSCP/dHPLC/sequencing for test-negatives with Elucigene FH20 + MLPA for test-negatives with sequencing (*LDLR*/*APOB*/*PCSK9*)	100 families	296	166 (56)
				DFH = 47	138	75 (54)
				PFH = 47	146	84 (58)
			Relatives: targeted sequencing in relatives	UFH = 6	12	7 (58)
Wiegman 2003[50a]	The Netherlands	Children of families with a documented *LDLR* mutation	Index parents: PCR/DGGE/sequencing/Southern blot of *LDLR*	591 families	806	617 (77)
			Targeted sequencing in children			
			LDLC ≥ 3.50 mmol/l for children (age and sex adjusted) without confirmed FH		228	131 (57)
			Targeted sequencing + LDLC ≥ 3.50 mmol/l for children (age and sex adjusted) without known FH		1034	748 (72)
Yarram 2010[38]	UK	Relatives	Index cases: Elucigene FH20 + SSCP/dHPLC/sequencing for test-negatives with Elucigene FH20 + MLPA for test-negatives with sequencing (*LDLR*/*APOB*/*PCSK9*)	104	27	15 (56)
			Cascade testing of relatives			

DFH, definite FH; PFH, possible FH; UFH, unclassified FH.

a The study by Wiegman and colleagues[50] also included children of families with plasma LDL-C levels above the 95th percentile for age and gender in a family with a history of PCVD in conjunction with tendon xanthomata.

that 27 relatives from 104 index cases were identified through cascade testing and 56% had a FH-causing mutation.

The fourth study, by Wiegman and colleagues,[50] used conventional sequencing of the *LDLR* gene in children of heterozygous (a documented *LDLR* mutation) or clinically diagnosed (plasma LDL-C levels above the 95th percentile for age and gender in a family with a history of PCVD in conjunction with tendon xanthomata) parents ($n = 591$) and reported 77% to have a FH-causing mutation. The authors suggested that the high proportion diagnosed might be due to the fact that siblings with very low levels of LDL-C were not referred to the paediatric clinic. Moreover, the paediatric hyperlipidaemic are less likely to have polygenic cases of hyperlipidaemia and are therefore more likely to have a higher mutation detection rate.

There were no studies using LIPOchip in relatives.

Other outcomes

Proportion with unequivocal diagnosis by Elucigene FH20 and LIPOchip *Table 16* gives the proportions with an unequivocal diagnosis by Elucigene FH20 and LIPOchip and the proportions that would subsequently require sequencing as reported in six studies.[36,37,39,41–43] Elucigene FH20 identified a mutation in only 16% of cases in a cohort of 635 clinically diagnosed FH cases, with > 80% still requiring sequencing for confirmation of diseases.[37] In Spanish studies, 46%[42,43] to 52%[39] were confirmed to have a mutation using LIPOchip. LIPOchip version 8 confirmed 29% of cases in a UK setting but in the same population 40% would be identified with a FH-causing mutation by LIPOchip version 10, with 60% still requiring sequencing.[41] Elucigene FH20 or LIPOchip detected, almost twice as many people with FH-causing mutations who were definite FH than those classed as possible FH (27% vs 11% in the study by Taylor and colleagues;[37] 51% vs 37% in the study by Tejedor and colleagues[43]).

Time taken to obtain test result Two studies on LIPOchip reported the time taken to obtain test results.[39,41] The time taken to obtain positive test results with LIPOchip (including data extraction and analysis) ranged from 10 days[41] to an average of 15 days.[39] Additionally, the time taken to detect rearrangements was 7 days and then 30[41]–45[39] days for sequencing. Palacios and

TABLE 16 Proportion with unequivocal diagnosis by Elucigene FH20 and LIPOchip

Study	Country	Test	FH diagnosis	Total tested	Number with unequivocal diagnosis (%)	Number requiring sequencing (%)
Hooper 2009[36]	Australia	Elucigene FH20	DFH	63	14 (22)	49 (78)
Taylor 2010[37]	UK	Elucigene FH20	DFH	190	52 (27)	138 (73)
			PFH	394	45 (11)	349 (89)
			UFH	51	5 (10)	46 (90)
			Total	635	102 (16)	533 (84)
Alonso 2009[39]	Spain	LIPOchip (195 Spanish mutations)	DFH or probable FH	808	419 (52)	389 (48)
Palacios 2010[41]	UK	LIPOchip version 8	NR	126	37 (29)	89 (71)
		LIPOchip version 10	NR	126	51 (40)	75 (60)
Stef 2009[42]	Spain	LIPOchip (247 mutations)	NR	2462	1140 (46)	1322 (54)
Tejedor 2005[43]	Spain	DNA array (118 mutations)	DFH	252	129 (51)	123 (49)
			Possible/ probable FH	155	58 (37)	97 (63)
			Total	407	187 (46)	220 (54)

DFH, definite FH; NR, not reported; PFH, possible FH; UFH, unclassified FH.

colleagues[41] reported that 2 months was required to obtain results by sequencing in conjunction with MLPA. An average of 68 days (range 10–93 days) was reported for obtaining complete results with the LIPOchip platform, with the majority of mutations being detected within 15–22 days after the start of the analysis.[39]

Subgroup analysis

Subgroup analysis by ethnicity The mutation detection rate may vary in ethnic groups as FH-causing mutations may be more frequent in one group of people than in another. The Elucigene FH20 and LIPOchip genetic tests are designed to detect mutations that are more frequent in European Caucasian populations.

Only the study reporting Elucigene FH20 by Taylor and colleagues[37] reported the detection rate of FH for ethnic groups. By using a sequence of tests in which Elucigene FH20 was used as a pre-screen followed by sequencing for test-negatives on Elucigene FH20 and then MLPA for test-negatives on sequencing, the mutation detection rate in a population of Indian Asian origin was 32.3% ($n = 31$) and in a population of African origin was 25% ($n = 8$). The study suggested that detection rates were lower for these groups than for white British groups, but the difference was not statistically significant ($p = 0.63$). The study population also comprised those of Middle East, Far East and non-British European origin, although detection rates for these groups were not reported.

In total, 10 out of 20 FH-causing mutations were identified in 31 patients of Indian Asian origin and only 1 out of 20 FH-causing mutations was identified in four patients of African origin. Only 3 out of the 10 mutations detected in the Indian Asian group were detected by Elucigene FH20.

Subgroup analysis by regions Taylor and colleagues[37] also reported the overall detection rate by CGA across six different centres in the UK. The detection of FH ranged from 8.3% to 73.6% among definite FH ($p = 0.001$) and from 21.7% to 39.5% for those with possible FH ($p = 0.13$). The authors further reported that when a centre with the smallest sample size was removed from the analysis the difference was no longer significant for the definite FH category ($p = 0.07$).

Familial hypercholesterolaemia detection according to type of gene Five studies reported FH detection according to the type of gene (*Table 17*). In patients with a genetic diagnosis of FH, most mutations detected by Elucigene FH20 or LIPOchip were in the *LDLR* gene (range 69–97%), followed by the *APOB* gene (range 3–27%) and the *PCSK9* gene [4% and 6% (two studies)].

Summary

In total, 15 studies (17 reports) were included. Three studies (four reports) evaluated Elucigene FH20, five studies (six reports) evaluated various versions of LIPOchip, four studies reported data on the performance of LDL-C as part of the Simon Broome criteria or LDL-C cut-offs of > 4 mmol/l and three studies reported age-and gender-specific LDL-C cut-offs for cascade testing of relatives. Five studies conducted in the UK recruited participants who had received a clinical diagnosis of FH based on the Simon Broome criteria, reporting Elucigene FH20, LIPOchip and age- and gender-specific LDL-C cut-offs. Three studies reported targeted gene sequencing for a mutation found in a family member.

Only studies reported as full-text papers ($n = 9$) were quality assessed. In the studies reporting Elucigene FH20 ($n = 1$) and LIPOchip ($n = 2$) and five of the six studies reporting LDL-C, the participants were representative of those who would receive the tests in practice. As Elucigene

TABLE 17 Familial hypercholesterolaemia detection according to type of gene

Study	Test	Total analysed	Total detected	Detected with *LDLR* gene, *n* (%)	Detected with *APOB* gene, *n* (%)	Detected with *PCSK9* gene, *n* (%)
Taylor 2010[37]	Elucigene FH20	635	102	70 (69)	28 (27)	4 (4)
Palacios 2010[41] Newcastle sample	LIPOchip version 8 + sequencing	120	65	52 + 1 CNC (80 + 2)	8 (12)	4 (6)
Stef 2009[42]	LIPOchip Spanish version (247 mutations)	2462	NR	94% + 6% CNC	0	0
Tejedor 2005[43]	LIPOchip earlier version (118 mutations)	407	187	181 (97)	6 (3)	NAn
Alonso 2009[39]	LIPOchip Spanish version (191 mutations)	808	537	521 (97)	16 (3)	NAn
	DNA array	808	419	403 (96)	16 (4)	NAn

CNC, copy number change; NAn, not analysed; NR, not reported.

FH20 and LIPOchip were used as a pre-screen with only test-negatives going on to receive further genetic tests, these studies suffered from partial verification bias, whereas in all of the LDL-C studies all of the participants who received the index test (LDL-C) also received a reference standard test. Patients received the same reference standard regardless of the index test result in 83% ($n = 5$) of the LDL-C studies but none of the Elucigene FH20 or LIPOchip studies (differential verification bias).

For Elucigene FH20, two studies, one by Taylor and colleagues[37] involving 635 participants and another by Yarram[38] involving 104 participants, reported 44% and 52% sensitivity, respectively, in detecting FH-causing mutations in patients with a Simon Broome clinical diagnosis of possible or definite FH. The kit had higher sensitivity in those with a clinical diagnosis of definite FH (49%) than in those with possible FH (40%).[37] Hooper and colleagues,[36] in a study set in Australia, reported a lower sensitivity of 29% for Elucigene FH20 in detecting FH-causing mutations in patients with a clinical diagnosis of definite FH based on the Dutch criteria.

Four studies reported the sensitivity of different versions of LIPOchip. LIPOchip version 10, containing mutations frequent in the UK population, showed sensitivity of 78.5% ($n = 126$) (based on hypothetical data received from the manufacturer) in detecting FH-causing mutations in those with a Simon Broome clinical diagnosis, whereas the LIPOchip version designed to detect 251 mutations that were not specific to the UK showed from 33.3% ($n = 22$) to 56.9% ($n = 120$) sensitivity. The sensitivity of two Spanish versions of LIPOchip containing 195 mutations and 247 mutations was reported as 78% ($n = 808$) and 95% ($n = 2462$), respectively, with the clinical diagnosis being made according to Dutch criteria or Dutch–MedPed criteria respectively.

One study reporting the performance of LIPOchip version 8 against CGA reported one false-positive, with specificity of 93.8%. In all other studies evaluating the performance of Elucigene FH20 and LIPOchip in detecting patients with FH-causing mutations, specificity was not calculable because none of the test-positives went on to receive CGA and therefore it was not known whether or not there were any false-positive results.

In two studies, the LDL-C test as part of the Simon Broome criteria had high sensitivity (90% and 93%) in detecting FH compared with a reference standard of CGA; however, both studies also reported high rates of false-positives, resulting in low specificity (28% and 29%). In these studies, LDL-C as part of the Dutch clinical diagnostic criteria was also shown to be highly sensitive

(88% and 99%) in detecting FH but with very low specificity (18% and 6%) compared with CGA. The reported sensitivity of LDL-C as part of the MedPed diagnostic criteria varied. Widhalm and colleagues[47] reported that the sensitivity of LDL-C cut-offs as part of the MedPed criteria was higher in children (81%) than in adults (66%) in detecting FH. Mabuchi and colleagues[46] reported higher accuracy of LDL-C cut-offs of 4.1 mmol/l (sensitivity 98.5%, specificity 98.5%) among genetically diagnosed FH patients and unaffected relatives.

Three studies reported data for age- and gender-specific LDL-C cut-offs for cascade testing compared with a reference standard of CGA. Lee and colleagues[48] reported sensitivity of 91% and specificity of 93% for cascade testing in a cohort from the UK. Starr and colleagues[49] reported sensitivities of 68%, 79% and 84% and specificities of 85%, 85% and 84% in cohorts of first-degree relatives from the Netherlands, Denmark and Norway respectively. Wiegman and colleagues[50] reported high sensitivity of 96% in children. Using an approach of targeted gene sequencing for a mutation found in a family member, 53–77% of relatives with FH were identified in different study populations. There were no studies using LIPOchip in relatives.

Chapter 3

Assessment design and results: cost-effectiveness

Review of cost-effectiveness studies

Search strategy

Two separate searches were conducted for studies considering the cost-effectiveness of any of the intervention tests (Elucigene FH20 or LIPOchip) for proband testing or for the cascade testing of relatives. Studies were sourced from searching a range of electronic databases and websites. This was supplemented with a quality-of-life search. Contact with experts in the field and the scrutiny of bibliographies of retrieved papers were also used to identify any additional studies. Highly sensitive electronic searches were conducted to identify reports of published studies on the cost-effectiveness of tests for FH in index cases and for cascade testing of relatives. The search focused on identifying RCTs and comparative studies and the results were restricted to articles written in English. The search strategy included searches of all relevant journals since inception.

The databases searched were MEDLINE (1948 to Week 1 2011), MEDLINE In-Process & Other Non-Indexed Citations (10 January 2011), EMBASE (1980 to 2011 Week 1), BIOSIS (1956 to 10 January 2011), Science Citation Index (1970 to 10 January 2011), Conference Proceedings Citation Index – Science (1990 to 10 January 2011), Centre for Reviews and Dissemination databases including Database of Abstracts of Reviews of Effects, NHS Economic Evaluation Database (NHS EED) and Health Technology Assessment database. Searches were also carried out of the Cost-Effectiveness Analysis Registry. A supplementary quality-of-life search was also undertaken, including MEDLINE (1948 to Week 1 2011), MEDLINE In-Process & Other Non-Indexed Citations (10 January 2011), EMBASE (1980 to 2011 Week 1) and IDEAS Economics and Finance Research (February 2011). Full details of the search strategies used and websites consulted are documented in *Appendix 3*. In addition, reference lists of all included studies were scanned to identify additional potentially relevant studies

Methods (inclusion and exclusion criteria)

Studies were deemed to be relevant for the cost-effectiveness review if they included a measure of cost-effectiveness of the intervention tests (Elucigene FH20 – or alternative earlier versions or LIPOchip version 8–version 10) relative to any of the included clinical diagnostic criteria (Simon Broome, MedPed or Dutch criteria). The population and setting for the studies retrieved for further investigation were as described in *Chapter 2*. In terms of outcomes, the preferred type of analysis was cost-effectiveness measured as cost–utility analysis [cost per quality-adjusted life-year (QALY) gained]. However, because of a lack of data, we also considered other measures of cost-effectiveness, including cost per case detected or cost per diagnostic accuracy measurement. Study type inclusion and exclusion criteria were limited as we did not want to exclude any potentially relevant studies at this stage, the principal requirement being that studies were for a population of index cases or relatives of index cases with a clinical diagnosis of FH. Titles and abstracts of all reports identified by the search strategy were screened. Full-text copies of all studies deemed to be potentially relevant were obtained and assessed for inclusion. Disagreements were resolved by consensus or arbitration by a local clinical advisor. A data extraction form was developed, with data extracted by one health economist. A second health

economist checked the data extraction and any disagreements were resolved by consensus among the review team. Additional further studies that did not meet our specific inclusion criteria but were none the less informative for development and population of the economic model were also retained. As these additional included studies did not form a vital part of the assessment, they have not been systematically critically appraised in depth but are included and narratively described in the following sections.

Results of the cost-effectiveness searches

A total of 258 papers were initially identified through the database searches, with a further 11 potentially relevant titles identified through the diagnostic accuracy search. However, on reading the titles and abstracts, only nine were judged potentially relevant to the cost-effectiveness review, with the remaining 260 not meeting the inclusion criteria of health economic analysis (cost-effectiveness or cost–utility) of a genetic test. We requested full-text articles of these nine papers that reported the cost-effectiveness of genetic testing and cascade testing techniques. These papers were further assessed by reading the full text of each retrieved paper and reapplying the inclusion and exclusion criteria. At this stage, only one study reported the cost-effectiveness of any of the comparators for this assessment. Of the remaining eight papers, three did not include any measure of cost-effectiveness and only briefly referred to cost implications, thus leaving a total of five relevant studies. Four of the five studies retrieved have been summarised in the previous systematic review undertaken as part of NICE clinical guidance CG71.[1] Data are extracted and published in appendix D of the clinical guidance document. The remaining study, which was not previously summarised as part of CG71,[1] is discussed below. In relation to additional searches for utility of diagnostic information, effect of mutation type on treatment choice and the efficacy of statins in children, potentially relevant full-text papers were retrieved and read in full, and have been considered in the economic modelling process and/or discussion where appropriate.

Discussion of included studies evaluating the cost-effectiveness of Elucigene FH20 and/or LIPOchip

One study[57] was identified that met our inclusion criteria and evaluated the cost-effectiveness of one of the intervention tests. This study assessed the cost-effectiveness of LIPOchip in identifying and testing first-degree relatives of index cases identified with FH in a Spanish population. The analysis also included subsequent treatment with statins of test-positive individuals. Screening and treatment management was compared with a strategy of no screening and the perspective of the analysis was that of the national health system (payer). Cost-effectiveness outcome was measured as incremental cost per life-year gained. Clinical diagnosis of at-risk individuals was based on a uniform protocol for clinical diagnosis and genetic testing of index cases was carried out using the LIPOchip platform, which included the following diagnostic steps:

1. LIPOchip DNA array
2. multiplex quantitative PCR used to identify significant gene rearrangements (applied if DNA array was negative)
3. complete sequencing of the *LDLR* gene (applied if the previous two steps were negative).

Among confirmed cases, the DNA array had a specificity and sensitivity of 99.7% and 99.9%, respectively, for all 118 mutations tested. Once index patients were identified, first-degree relatives were tested using steps 1 and 2 above only. Effectiveness among relatives was based on relative risks adjusted for age and sex[59] and applied to national mortality rates. Once identified and treated, it was assumed that mortality risk reduced relative to untreated patients. The total cost of detecting a positive case was €1447 based on the assumption that, to detect one positive case, 3.4 relatives would need to be tested. This was combined with treatment costs based on simvastatin 40 mg and costs of acute myocardial infarctions (MIs) avoided based on risks

calculated from Wonderling and colleagues.[59] The cost-effectiveness was thus estimated based on cost per life-year gained as €3243 in the base-case analysis. Sensitivity analyses conducted varied the incremental cost-effectiveness ratio (ICER) from €1073 to €7235 per life-year gained. Probabilistic analyses indicated a 95% probability of cost-effectiveness at a societal willingness to pay for a life-year gained of > €7400 and a probability of 45% at a willingness to pay of €3450. The results suggest that genetic screening of first-degree relatives with LIPOchip in Spain is a cost-effective use of resources. The main limitation to this study in terms of this assessment is that there is no active comparator – it is assumed that no screening would take place in routine care. However, the study is useful and informative regarding the potential of LIPOchip. No studies were available reporting on cost-effectiveness for any of the other intervention tests.

Discussion of supplementary cost-effectiveness evidence

The remaining supplementary papers detailing cost-effectiveness of cascade testing among relatives using targeted cascade testing and other methods are briefly summarised and discussed below. Full data extraction pertaining to these reports is available from the NICE website as appendix D to the NICE clinical guideline document CG71.[1] None of these studies evaluated the cost-effectiveness of any of the tests specifically in index patients; however, all indicated cost-effectiveness of cascade testing for FH among relatives of known FH index patients. The five included studies are discussed briefly below.

Marang-van de Mheen and colleagues[60] compared five screening options in the Dutch population compared with no screening: treating (1) all patients with cholesterol level > the 95th percentile for the general Dutch population; (2) individuals fulfilling treatment criteria based on Dutch Institute of Health Care Improvement guidelines on hypercholesterolaemia; (3) (1) above but only those untreated at screening; (4) (2) above but only those untreated at screening; and (5) all FH-positive patients. The Framingham equation[61] was used to estimate risk, survival and costs and the economic outcome measure is cost per life-year gained. This is explicitly not recommended as part of CG71[1] for calculating risk in the Simon Broome population. The most cost-effective option is option (2) with an associated ICER of €24,376 per life-year gained. Discounting was not conducted and there are questions relating to generalisability to a NHS perspective.

Marks and colleagues[62] completed a cost-effectiveness analysis of screening for FH patients aged 16–24 years from the perspective of the NHS. Strategies evaluated were universal screening, opportunistic screening (unrelated reasons), opportunistic screening (patients with premature MI) and full screening of all first-degree relatives diagnosed with FH. The main comparison for the analysis was no screening. The primary outcome measure was cost per life-year gained and the study showed that tracing family members (first-degree relatives) systematically was the most cost-effective strategy with an ICER of £3097 per life-year gained.

Marks and colleagues[63] conducted additional work over a 10-year period estimating the cost-effectiveness of (1) family tracing of index cases and (2) systematically screening all 16-year-olds. Primary economic outcomes were cost per case detected and cost per death averted. The main comparison for the analysis was no screening and no incremental analyses were conducted between groups. Costs per case identified were £3505 (family tracing) and £13,141 (universal screening). Costs per death averted were £3187 and £1.6M for the family tracing and universal options respectively. Therefore, the authors conclude that a more targeted screening programme identifying relatives of index cases is more cost-effective.

Wonderling[59] used data from the Dutch screening programme from year 2000 in a sample of 18- to 60-year-olds to estimate the cost-effectiveness of screening compared with no screening. Treatment was administered using statins and it was estimated that screening would prevent

26 MIs per 100 patients receiving statin therapy. Primary outcome measures for the economic analysis were cost per case detected and cost per life-year gained, which were $7500 and $8800 respectively. Results were sensitive to the price of statins and a worst-case scenario estimated that the ICER could increase to $38,300 per life-year gained.

The additional included study was an older version of the currently included Marks study.[64] Therefore, the up-to-date data have been reported. Other studies, including those by Leren,[65] Humphries and colleagues[66] and Hadfield and colleagues[67] all suggest that genetic screening is a cost-effective use of NHS resources and should be implemented across the UK.

The main background for the economic modelling of these candidate tests comes from NICE clinical guideline CG71,[1] in which an economic model was developed to compare DNA testing with LDL-C testing. The results showed that DNA testing was cost-effective with an associated ICER of £2676 per QALY gained. This model has been updated and integrated to account for the testing of Elucigene FH20 and LIPOchip and other plausible scenarios for the identification of FH and is described in more detail in the following sections.

We did not identify any other health economic models for the identification of FH that would be informative to the development of this assessment.

Summary

NICE clinical guidance (CG71)[1] concluded that genetic testing of relatives of index cases with FH is cost-effective. There was, however, no available evidence detailing the cost-effectiveness of genetic testing of index patients specifically using any of the candidate tests in this review (i.e. Elucigene FH20 or LIPOchip). One study evaluated the cost-effectiveness of an intervention test for cascade testing of relatives.[57] This is cascade testing based on LIPOchip; however, there are less costly methods of cascade testing of relatives (targeted sequencing) and so this analysis may be of limited use for informing the economic evaluation for this appraisal. A number of supplementary studies discussed provide strong evidence that cascade testing of relatives of index cases with FH is cost-effective. Based on this evidence together with the results of CG71,[1] we have developed an economic model to assess the cost-effectiveness of Elucigene FH20, LIPOchip and comparators (including CGA and LDL-C) for the identification and treatment of index cases with FH and the identification of relatives by cascade testing.

Methods for economic analysis

The care pathway for this economic evaluation has been defined by NICE clinical guidance (CG71)[1] and is as summarised in *Chapter 1* (see *Care pathways*). In brief, the key points set out in this guideline that have implications for the economic evaluation recommend:

- DNA testing to confirm clinical diagnosis of FH based on Simon Broome criteria in index (proband) patients suspected of having FH. A clinical diagnosis will include two LDL-C concentration measurements.
- DNA testing for identified mutations in first-, second- and possibly third-degree family relatives.
- Patients identified with FH should be offered a high-intensity statin therapy option.

A number of diagnostic pathways were specified as part of the NICE scope and review group protocol for analysis and are used to develop the economic modelling for this assessment; they are presented in *Table 18*.

TABLE 18 Diagnostic strategies for identifying a genetic mutation (or LDL-C level) in index cases

Strategy[a]	Stage 1	Stage 2	Stage 3
1	Clinical diagnosis of FH (LDL-C test required)	Elucigene FH20	Treatment decision for index case and initiation of cascade testing for test-positive first-, second- and possibly third-degree biological relatives of the index case
2		LIPOchip	
3		CGA	
4		Elucigene FH20 then LIPOchip for negatives	
5		Elucigene FH20 then CGA for negatives	
6		LIPOchip then CGA for negatives	
7		Elucigene FH20 then LIPOchip for negatives then CGA for negatives	
8		Elucigene FH20 then MLPA for negatives	
9		LIPOchip then MLPA for negatives	
10		Elucigene FH20 then LIPOchip for negatives then MLPA for negatives	
11		LDL-C test	

a LIPOchip platform (processed in Spain).

Using these care pathways we developed an economic model to estimate the cost-effectiveness of several diagnostic strategies for the confirmation of clinical diagnosis of FH among index cases and the subsequent identification and treatment of FH-positive first-, second- and third-degree biological relatives of the index case.

Model structure

The model structure was developed based on clinical advice in line with the NICE scoping document and assessment group protocol. As diagnostic strategies in themselves do not lead to quality-of-life implications directly, the model follows a linked evidence approach in which intermediate outcomes (diagnostic accuracy) are linked to treatment outcomes and hence QALY gains. By a linked evidence approach we mean that, based on diagnostic test result, a patient will be either positive or negative. Positive-testing patients receive a high-intensity treatment and negative-testing index cases receive a low-intensity treatment as they will still be at risk of cardiovascular events based on high LDL-C levels. The treatment received by each group (true-positive, true-negative, false-positive, false-negative) will determine their cardiovascular events avoided and hence their QALYs gained from that treatment decision. The outcomes on the index diagnostic test also determine whether or not the relatives will receive targeted sequencing in combination with LDL-C or LDL-C alone as the cascade test of choice. Therefore, we can say that the diagnostic test outcome of the index case is 'linked' to treatment choice and overall health outcomes over a lifetime horizon.

A decision tree model has been developed to identify the most cost-effective method of identification of index cases and subsequent testing and identification of at-risk relatives. Diagnostic accuracy outcomes are linked to treatment outcomes and hence QALY gains using a previously developed economic Markov model used for clinical guidance (NICE CG71[1]).

One of the most important advantages of genetic testing is the identification of family members for cascade testing. The test used to cascade test relatives of index cases will depend on the test used to identify the index case. Three tests (targeted gene sequencing, LIPOchip and Elucigene FH20) are substantially cheaper than CGA and may be used for cascade testing. For the majority of genetically confirmed index cases, targeted sequencing for the culprit mutation is the most commonly applied genetic cascade testing method (Dr Zosia Miedzybrodzka, University of Aberdeen, 2011, personal communication). For relatives of index cases identified using the

Elucigene FH20 or LIPOchip tests, the cheaper test designed to detect the identified mutation (LIPOchip, Elucigene FH20 or targeted sequencing) may be used to cascade test relatives. LIPOchip or Elucigene FH20 may also be used to cascade known mutations picked up on other tests that would also be detected by the candidate tests.[68] This scenario would apply only if LIPOchip or Elucigene FH20 were cheaper than targeted sequencing. For index cases identified based on Simon Broome criteria and not a genetic test, then LDL-C concentration measurement is the most common method used to cascade test relatives. The model structure for relatives assumes that, once a patient has a confirmed diagnosis, his/her close relatives will be identified and cascade testing will begin, first testing all first-degree relatives. For the base-case analysis it is assumed that each index case will have on average five first-degree relatives and each first-degree relative will have on average a further two first-degree relatives (second-degree relatives of each index case) who will require testing. For the purposes of this assessment we assume that once a first-degree relative tests positive, the process moves on to second-degree relatives and similarly on to third-degree relatives if appropriate. If a first-degree relative tests negative for FH, then the cascade testing process stops irrespective of the test used for cascading.

A copy of the model decision tree is illustrated in *Figure 9*, detailing the identification strategies for index cases in the model. Each circle represents a chance node at which probabilities of positive and negative test results are assigned. Index cases receive cost and QALY payoffs at each terminal node (triangle), at which point relatives are identified for cascade testing as described above.

Identification of probabilities for the decision model

The probabilities used to populate this model were estimated using standard conventions of Bayes' theorem. Basically, once we know the sensitivity and specificity of a test as well as the a priori probability of disease in the target population, we can calculate positive, negative, true-positive, true-negative and thus false-positive and false-negative values for the model. The formulae used for the calculation of each branch of the tree for single test strategies (e.g. CGA alone) are described in *Table 19*.

When tests are connected in series as add-ons to each other (i.e. the second test detects the same mutations as the first test plus additional FH-causing mutations), the theory is essentially the same but will be represented by the associated values of the second test. Taking Elucigene FH20 followed by CGA as an example, the positive rate will be [(proportion testing positive on Elucigene FH20 + proportion testing positive on CGA) – proportion testing positive on Elucigene FH20]. The proportions testing positive on Elucigene FH20 cancel each other out as they are incorporated in CGA and CGA detects all the mutations detected by Elucigene FH20 and more; therefore, the proportion testing positive on this example strategy is simply the value of the most comprehensive test in the strategy (i.e. CGA). A similar argument applies to Elucigene FH20 followed by LIPOchip.

For strategies in which MLPA is used as an add-on test to Elucigene FH20 or LIPOchip, the calculations are slightly different. As MLPA detects additional cases not detected using Elucigene FH20 or LIPOchip (we assume here that the detection of deletions and duplications on LIPOchip is inadequate and MLPA will still be needed to give a more robust estimate), the effect of the two tests in series is not as before. Therefore, for the calculation of true-negatives on Elucigene FH20 followed by MLPA, the effect will be multiplicative and can be calculated as [(1 – prevalence) × (specificity of Elucigene FH20) × (specificity of MLPA)]. The MLPA test has not been considered separately from CGA because, by definition, CGA will already include MLPA as part of the process.

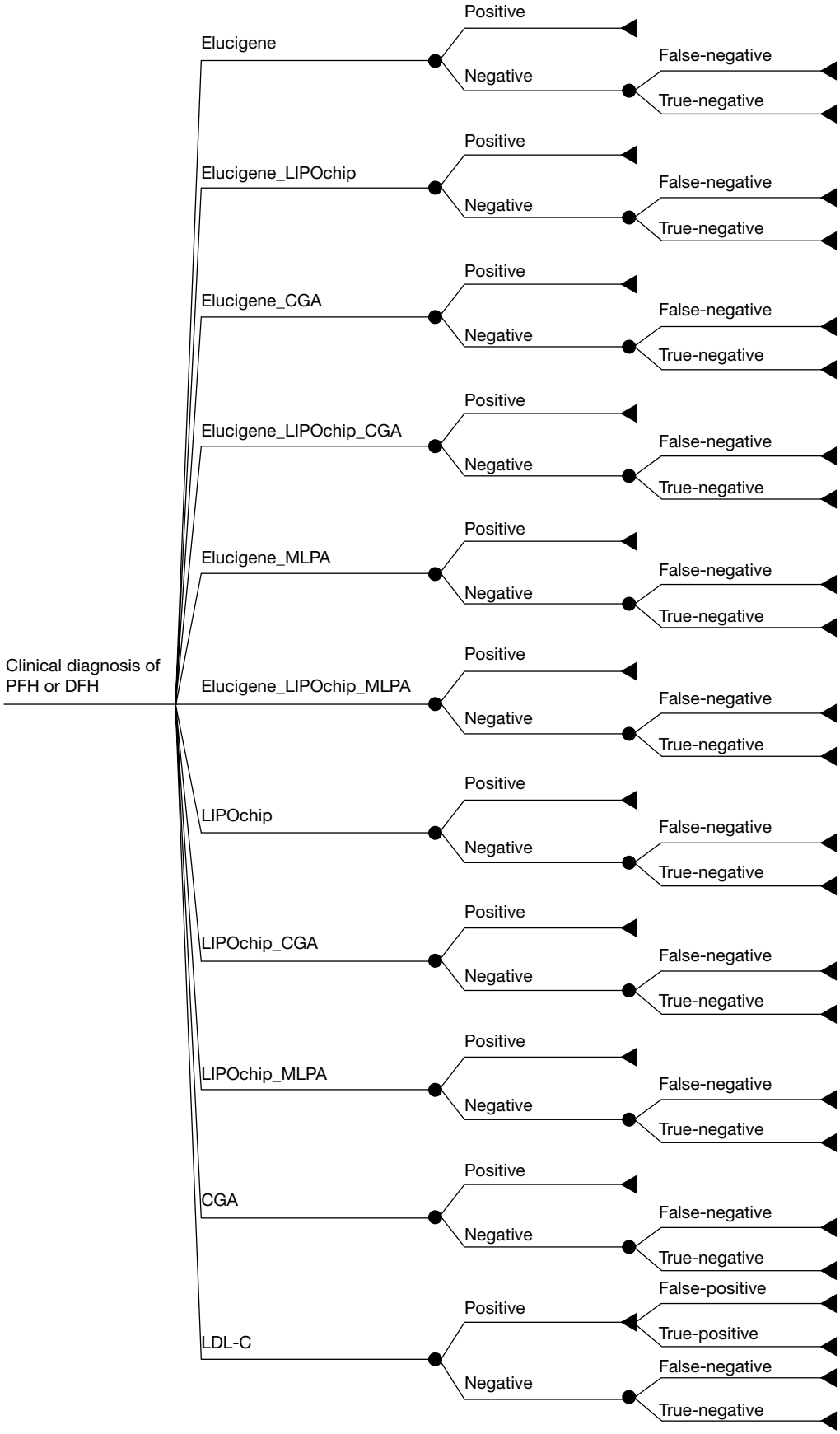

FIGURE 9 Economic decision tree model for index cases. DFH, definite familial hypercholesterolaemia; PFH, possible familial hypercholesterolaemia.

TABLE 19 Calculation of probabilities for decision tree

Test results for decision tree	Calculation
Positive	Sensitivity × prevalence + (1 – specificity) × (1 – prevalence)
Negative	1 – positive
False-positive	1 – PPV
False-negative	1 – NPV

NPV, negative predictive value; PPV, positive predictive value.

Sensitivity and specificity values used in the calculations of the model are presented in *Table 20* for information. More detailed information on sensitivity and specificity for all included studies is presented in *Chapter 2*. Studies chosen to inform the economic modelling fulfilled two main criteria: (1) they were based on patients with a Simon Broome definite FH or possible FH clinical diagnosis of FH (preferably in a UK population) where possible and (2) when tests were conducted in a number of different countries (outwith the UK) in a study, we have chosen the cohort with the largest sample size (unless some explicit reason existed why this would not be appropriate). These were assumed to offer the most robust estimates in the absence of UK data. When studies did not report clinical diagnosis based on the Simon Broome criteria or when evidence was of poor quality and limited usability, we obtained parameter values from Dutch and MedPed criteria instead. For reasons discussed in the statistical analysis, it has not been possible to pool estimates of sensitivity and specificity for a combination of definite FH and possible FH diagnoses across studies in a robust way because of study heterogeneity (see *Chapter 2*, *Assessment of test performance*). Therefore, single studies have been chosen based on the best available evidence and the most recent version of each test analysed. The impact of these choices on our base-case conclusions will be explored through the use of lowest and highest estimates available from all of the included studies, based on all clinical criteria (MedPed and Dutch criteria included), in sensitivity analysis.

It is important to note that there is likely to be some correlation between those patients detected on MLPA and those detected using LIPOchip. Clinical expert opinion (Dr Zosia Miedzybrodzka, University of Aberdeen, personal communication) suggests that the LIPOchip test may be inadequate to detect deletions and duplications and in practice MLPA may be required to give a more accurate diagnosis.

LIPOchip can be used within the model in two separate ways. First, the strategy 'LIPOchip' refers to the test purchased by a laboratory in the UK from the manufacturer and processed at the UK laboratory. Additionally, the manufacturer offers a service whereby blood samples can be sent to the manufacturer's plant in Spain for analysis using a two-stage process, first testing with LIPOchip and then sequencing of the *LDLR* gene for those testing negative. This is referred to as LIPOchip platform (Spain). Because of its second stage, at an additional cost of €100, this test has a higher sensitivity. It is, however, not CGA as the process does not include MLPA. Therefore, the sensitivity is less than that of CGA. Clinical expert opinion in the UK suggests that, to be able to fully detect all deletions and duplications of the gene, the MLPA test would be required as LIPOchip's own method of detecting these cases may be inadequate. Additional data presented at the spring meeting of the CMGS[70] suggest that (using data from Bristol's NHS Hospital Genetics Laboratory) LIPOchip version 10 may be inadequate to detect copy number changes compared with MLPA, with only two cases out of a sample of seven correctly identified using LIPOchip.

In addition, there is much debate about the true prevalence of detectable FH-causing mutations among patients testing positive (definite FH or possible FH) based on the Simon Broome

TABLE 20 Sensitivity and specificity of tests used to populate the economic model

Test	Sensitivity[a]	Specificity[a]	Source used for economic modelling	Justification for choice of source
Elucigene FH20	0.44	1	Taylor 2010[37]	This is the most up-to-date test for Elucigene FH20
LIPOchip	0.79	1	Palacios 2010[41]	Only available data based on UK version 10 of LIPOchip
CGA	1	1	Assumption	Based on clinical expert opinion, this will correctly detect all known mutations causing FH; it is assumed, therefore, that if a patient tests negative he/she will not have FH
LDL-C (Index)[b]	0.90	0.29	Damgaard 2005[45]	This was the best available data based on Simon Broome criteria
LDL-C (Relatives)	0.68	0.85	Starr 2008[49] the Netherlands group	The Netherlands group chosen as it represented the greatest number of patients being tested (sensitivity analysis explores high and low estimates of both sensitivity and specificity based on all studies)
MLPA[c]	0.12	1	Calculation	Relates to a stand-alone detection rate of approximately 5%, confirmed through clinical expert opinion (Dr Gail Norbury, Guy's Hospital, London, 2011 and Dr Zosia Miedzybrodzka, University of Aberdeen, Aberdeen, 2010)

a Comparator for calculation of sensitivity and specificity is CGA; values are rounded to two decimal places.
b Note that the comparator for the Damgaard study was just complete genetic analysis of the LDLR and APOB genes and did not include the *PCSK9* gene.
c The sensitivity for MLPA is not used for MLPA as a stand-alone test in the model as this would not happen in clinical practice. The sensitivity reported here is used to calculate the sensitivity of test strategies such as Elucigene FH20 followed by MLPA for negatives, in which MLPA might be expected to add to the sensitivity of the main test.

criteria. There is also great variation in this number between laboratories and this is likely to be because of issues of ethnicity as some tests will have different detection rates based on different ethnic groups (see *Chapter 2*, *Assessment of test performance* for additional information). For the purposes of our base-case analysis, we have assumed that 36.5% of clinically diagnosed patients (Simon Broome definite FH or possible FH) will have an identifiable mutation.[37] Data from four regional Scottish genetics services (Aberdeen, Dundee, Edinburgh and Glasgow; Dr Zosia Miedzybrodzka, University of Aberdeen, 2010, personal communication) suggest that, between 2007 and 2010, this value was approximately 35% for the whole of Scotland based on data classifiable as definite FH or possible FH. This has been confirmed in personal communication with Dr Zosia Miedzybrodzka, who estimates that, for every three patients tested in Aberdeen using CGA, on average only one will have a detectable FH-causing mutation. NICE CG71[1] estimates, using data extracted from the UK FH Cascade Audit Project (FHCAP),[70] that 80% of patients clinically diagnosed with definite FH will have a detectable FH-causing mutation and 30% of those diagnosed as possible FH will have a detectable mutation. Given that the FH audit 2010[18] identifies 36% as definite FH and 58% as possible FH (the remainder being homozygous or not stated), this would suggest that 46.2% of patients clinically diagnosed as definite FH or possible FH would have an identifiable genetic mutation using CGA. Other studies quote varying estimates of these values and so maximum and minimum values will be explored in the sensitivity analysis. It is estimated that 50% of first-degree relatives of an index case will have an inherited mutation. This evidence for first-degree relatives has been applied to second- and third-degree relatives in the model. The reason for this is that the process of cascade testing is an iterative approach. Second-degree relatives will not be tested using targeted sequencing unless a first-degree relative has an identified mutation. Therefore, it is assumed that the second-degree relative is in fact the first-degree relative of an individual with an identified FH-causing mutation and so will also have a 50% probability of having inherited that mutation.

Markov model

The Markov model for this assessment has been adapted from the model used for the estimation of treatment effect used to inform NICE CG71.[1] The model was developed by the Royal College of Physicians Guideline Development Group and is updated in this assessment. This model calculated the lifelong treatment costs and outcomes of high-intensity statin therapy for the management of FH and low-intensity statin therapy for the management of others at risk of CHD because of elevated lipid levels. In addition to those who were classed as well, a total of eight further health states were modelled [unstable angina, MI, peripheral arterial disease (PAD), stroke, heart failure, revascularisation, cardiovascular death and other death]. Baseline risks were sourced from NICE technology appraisal 94[71] and relative risks were sourced from the Simon Broome register. Utility weights were sourced from the literature and validated by the health economist working on this assessment. Utility of the general population was taken from the Health Survey for England 1996,[72] which is the most up-to-date data source for the UK general population, and was adjusted for age and sex differentials. Beneficial health outcomes were used to estimate QALYs based on reduced risks of cardiovascular incidents. These treatment effects were sourced from a meta-analysis of two RCTs, the Incremental Decrease in Clinical Endpoints Through Aggressive Lipid Lowering (IDEAL) and the Treating to New Targets (TNT) trials conducted as part of the NICE CG71 assessment.[1] Data from Versmissen and colleagues[8] were checked against and found to be consistent with the assumptions and data used for CG71,[1] in so far as they show the efficacy of statins in improving the clinical causes of cardiovascular disease and by extension the reduction in serious cardiovascular events such as MI. However, they do not describe the exact causal relationship between the improved clinical outcome and reduced events. The data from Versmissen and colleagues[8] are consistent with those of the CG71[1] assessment in that they suggest efficacy of statins and by extension the reduction in serious cardiovascular events such as MI. Costs and outcome data have been updated to current values using the latest available literature in the field or inflated to current prices (2010/2011) if no updated literature was available. Further details of the model structure are available from the NICE website (appendix E to the clinical guideline document[1]). The perspective of this economic evaluation is that of the UK NHS and all costs and resource use are applied in accordance with NICE guidelines on the methods of technology appraisal. NICE recommends that, where possible, the desired economic outcome is cost per QALY gained. Treatment costs and QALYs gained are extrapolated to the patient's lifetime horizon and discounted at a rate of 3.5% per annum in line with standard NICE methods. It was not deemed necessary to discount diagnostic costs for each individual as the time taken for diagnosis is < 1 year. Sensitivity analyses explore the impact of varying the discount rate for both costs and QALYs between 0% and 6%. All other follow-up clinical costs that are expected to occur annually once a diagnosis of FH has been made are discounted as described.

Relevant patient populations

The relevant patient population for the base-case analyses is adults with heterozygous FH, focusing on index patients with a clinical diagnosis of FH based on the Simon Broome criteria (either definite or possible FH). Sensitivity and specificity of the tests included for the economic modelling both implicitly account for patients with either definite or possible FH. Data showing separate sensitivity and specificity rates for definite FH and possible FH were not available for all tests under consideration, thus making accurate subgroup analysis difficult. The data that were available are detailed in *Tables 9–14* (index cases) and *Table 15* (testing of relatives). Children with a clinical diagnosis are considered as a separate age subgroup in line with current CG71 recommendations.[1] Patients with an identified mutation causing FH are informed of their diagnosis and first-, second- and third-degree biological relatives are identified. Sensitivity analysis explores a situation in which only first- and second-degree biological relatives are cascade tested.

Treatment options to be evaluated

Treatment options to be evaluated are based on NICE CG71,[1] which recommends that a patient with FH should be offered a high-intensity statin therapy for the aggressive lowering of lipid levels by a recommended 50%. Index cases who have elevated lipids on the basis of the Simon Broome criteria (i.e. the majority of patients) will benefit from statin therapy as they are at a ≥ 20% 10-year risk of cardiovascular disease events.[71] We assume that 10% of relatives testing negative on targeted sequencing will also require some cholesterol-lowering therapy. This is an author assumption based on clinical expert opinion and previous NICE guidance and is varied between 0% and 50% in the sensitivity analyses. This refers to the estimated percentage of relatives without an identified mutation who will require treatment on the basis of high cholesterol levels. Such cases receive a low-intensity treatment in the model. As relatives are not clinically diagnosed with FH based on the Simon Broome criteria, it would be inappropriate to treat all patients, as only a percentage will have elevated lipids. The impact of varying this assumption is explored in sensitivity analysis. There is, however, much debate among clinicians over how to treat FH and patients at an increased risk of cardiovascular disease as a result of elevated lipids, with some choosing a 'start low' treatment option (starting all patients on a low-intensity statin such as simvastatin 40 mg) and others giving everyone a high-intensity statin (e.g. atorvastatin 80 mg or rosuvastatin). For the base-case analysis, we have assumed a multitreatment regimen for FH patients based on and adapted from the FH clinical audit 2010.[18] Patients with a Simon Broome-positive diagnosis but who have no genetic confirmation of FH will receive low-intensity statin therapy to reduce their elevated lipid levels. Such cases (especially those relatives who are false-positive) may also respond adequately to exercise and diet therapy, the effects on quality of life of which are beyond the scope of this assessment. Cole and colleagues[73] have conducted a detailed systematic review of the literature to explore the evidence in relation to the effects of dietary and lifestyle interventions in chronic heart disease risk reduction. Also, NICE guidance on dietary interventions in CHD provides additional information in the UK. Personal communications from Dr Anthony Wierzbicki (2011, Guy's and St Thomas' Hospitals NHS Trust) and Dr William Simpson (2011, NHS Grampian) are used in sensitivity analyses to explore the sensitivity of the model to treatment choice in practice.

Resource use estimation

Clinical resource use

For the purposes of this evaluation, we have assumed that all index cases will have received a clinical diagnosis of FH based on the Simon Broome criteria. Resource use and costs associated with this diagnosis are common to all tests being evaluated and so are not included. This is standard economic evaluation practice to include only resource-use estimations which differ between tests under consideration. However, the resource use associated with tests after the initial diagnosis is important and has been considered in the analysis. It is assumed that, once the proband has a genetic test or LDL-C confirmation of FH, he or she will attend a lipid clinic to discuss treatment and lifestyle management of the condition. It is at this point that family pedigree will be identified and contact with relatives will be initiated. It is assumed that initially only first-degree relatives will be contacted as there would be no point in contacting second-degree relatives until a diagnosis was confirmed in first-degree relatives using a genetic screen. *Table 21* details resource use and cost estimation for this process based on clinical expert opinion and Hadfield and colleagues.[70]

Index cases or relatives diagnosed with FH are offered an annual follow-up appointment with a lipids specialist at an outpatient clinic. In the absence of a specific unit cost tariff for a lipids specialist, this service is assumed similar to a cardiologist appointment (Dr William Simpson, University of Aberdeen, 2011, personal communication) and is costed at £222 per outpatient consultation.

TABLE 21 Resource use of health-care professionals for both index and cascade testing of patients after diagnosis

Health-care professional	Unit cost/ hour (£)	Time (hours) index case	Cost index case (£)	Time (hours) relatives	Cost per relative positive (£)	Cost per relative negative (£)	Source for unit costs
Consultation with lipid specialist	222.00		222.00		222.00	0	PBR, cardiologist, first attendance[74]
Clinical nurse specialist, grade 7, to confirm family pedigree and discuss	57.00	1.86	106.02	1.20	68.40	68.40	PSSRU 2010,[75] cost per hour of client contact, Hadfield 2008[70]
Clerk time to initiate contact with relatives[a]	26.00	0.25	48.75	0.25	39.00	0	PSSRU 2010,[75] band 5 administrator
Cost of consumables to initiate contact with relatives	0.78		5.85		4.68	0	Cost per letter, NICE CG71[1]
Two lipid profile tests to confirm diagnosis	8.00		16.00		16.00	16.00	Personal communication, Dr William Simpson, 2011, NHS Grampian
Cost of processing the lipid tests	1.60		3.20		3.20	3.20	PBR national tariff for clinical biochemistry[74]
Cost of GP consultation to take second cholesterol measure for confirmation	36.00		36.00		36.00	36.00	11.7 minutes, surgery consultation, PSSRU 2010[75]
Total			**438.00**		**389.00**	**124.00**	

PBR, Payment by Results; PSSRU, Personal Social Services Research Unit.

a Calculations for cost of index case and relatives are based on an average of 1.5 letters sent for each relative of an index case. Assuming the average index case has five first-degree relatives, and the time taken per letter is 0.25 hours, then the cost is £26 × 0.25 × 1.5 × 5 = £48.75. Similarly for the cost per positive relative, again an average of 1.5 letters per first-degree relative and an average of four contacts for a positive case, the resultant cost is £26 × 0.25 × 1.5 × 4 = £39.00.

Diagnostic resource use

A new national activity unit has been developed for molecular genetics and cytogenetic tests in the UK. This is based on a weighted report and uses for molecular genetics an amplicon as the base unit. All molecular genetic tests are then assigned a relative number of units that slot into bands with some efficiency built in as the number of amplicons increases. This new methodology for measuring activity for molecular genetic tests was developed by collaboration between the CMGS and the UKGTN. The objective was to devise a transparent and consensus system for measuring molecular test activity that could be implemented by all laboratories. Tests are weighted by complexity so that, for example, simply booking in a sample has the lowest weight and sequencing a gene of over 100 exons, for example *RYR2*, the highest. All realisable costs of each laboratory are collated and a total cost of the service is then calculated including salaries, consumables, overheads, etc. Each laboratory can derive its own unit cost, based on dividing budget by activity, and thus in effect derive a cost per test. For example, a £1.2M service producing 30,000 MOLUs will have a unit cost of £40.00. This system of pricing has been modelled by most of the laboratories in the UK and has been accepted by the professional bodies and UKGTN as a suitable approach to establishing a national tariff for genetic tests. Details of the national MOLU bands are included in *Appendix 11* for information. The MOLU system is not a perfect system of estimating costs, however, and the limitations are outlined in *Chapters 1* and *5*.

For the base-case analysis, transportation costs of samples (preferably blood samples) for DNA testing and blood samples for LDL-C testing are included. Based on clinical expert advice

(Dr Gail Norbury, Guy's Hospital, London, 2011, personal communication), an increasing number of genetics samples are tested by processing saliva samples. Saliva-based samples are less costly to transport as they are more stable and require only first-class postage; however, the kits to extract the DNA are substantially more expensive. These resource use differences, however, will be included in the MOLU consumables mentioned above based on 1 MOLU for DNA extraction. The majority of tests are carried out in the UK; however, LIPOchip may be processed by the manufacturer on site in Spain. The additional resource and transportation costs associated with sending a blood sample overseas via air are considered for the LIPOchip platform processed in Spain. This was assumed to take a cost of 1 MOLU, commonly applied in genetic testing to cost transferring samples to laboratories overseas. Therefore, a cost of £30 has been applied in the base case. Additionally, there may be extra costs associated with resampling an estimated 3% of samples (Progenika, 2011, personal communication). These costs are also incorporated.

Unit cost estimation

Clinical costs

Costs of clinician time for treating patients, identifying a family pedigree, counselling relatives on the importance of their condition and contacting relatives themselves are estimated using Payment by Results (PBR) national tariffs where available (e.g. for a first appointment with a lipid specialist). For all other resource use, including clinical nurse specialist (to identify pedigree and counsel patients), GP time to confirm second LDL-C test and administrator time to contact relatives, costs are estimated using Personal Social Services Research Unit (PSSRU) unit costs of health and social care.[75] Costs are based on the median of the appropriate agenda for change pay scale and include overheads, training costs, insurance, annual leave, etc.

Diagnostic costs

Costs of genetic testing strategies vary greatly among laboratories, especially based on their area of expertise and also in relation to their size – the greater the laboratory size, the greater the throughput of samples tested and thus the lower the costs based on economies of scale through mass genetic testing. Laboratories that can keep their budget constant or can reduce it but increase the number of MOLUs produced will have lower unit costs. The incentive then is to reduce the total budget while maintaining or increasing output. This system is simplistic and transparent and is the method adopted by most laboratories in the UK in setting their genetic testing tariffs (Dr Zosia Miedzybrodzka, University of Aberdeen, and Dr Gail Norbury, Guy's Hospital, London, 2011, personal communication). For the purposes of the base-case analysis, it is assumed that the MOLU cost is £30 per MOLU (Dr Kevin Kelly, University of Aberdeen, 2011, personal communication). The cost of each MOLU will be varied in sensitivity analysis provided by Dr Gail Norbury (£33 per MOLU). Unit cost estimation is adjusted within the model for strategies that have more than one test in order to account for the cost differentials associated with earlier positive test identification. The cost of DNA extraction is also incorporated into the analysis and receives a unit of 1 MOLU. Details of MOLU units applied and the associated costs for each test strategy are presented in *Table 22*. The cost of testing a hypothetical cohort of 1000 index cases with combination strategies is dependent on the numbers testing positive on the first test in that strategy. For example, in a strategy such as Elucigene FH20 followed by CGA for negatives, an index case who tests positive on Elucigene FH20 will not receive the second more comprehensive test.

In addition to the tests outlined above, the LIPOchip platform (Spain) as a genetic testing platform is a potential alternative to CGA. The test, which involves using the LIPOchip followed by sequencing of test-negative cases, is offered by the manufacturer (Progenika) at a cost of €250 for a LIPOchip test and €350 for the whole process. The associated costs are incorporated into the analysis using an exchange rate of €1 = £0.89. The LIPOchip platform processed in Spain is explained in *Chapter 1*. Briefly, this is a two-stage process whereby, if the sample is positive on LIPOchip, no further testing takes place. If the sample is negative on LIPOchip

TABLE 22 Costs applied to each testing strategy in the model

Testing strategy	MOLUs test 1 (including extraction)	Number positive test 1[a]	Number receiving test 2	MOLUs test 2	Number positive test 2[b]	Number receiving test 3	MOLUs test 3	Total MOLUs for a cohort of 1000 index cases tested[c]	Total cost per MOLU	Total cost (£)
Elucigene FH20	5	161						5000	30	150,000
LIPOchip	11	287						11,000	30	330,000
CGA (including MLPA)	16	365						16,000	30	480,000
Elucigene FH20 followed by LIPOchip for negatives	5	161	839	10	126			13,390	30	401,700
Elucigene FH20 followed by CGA for negatives	5	161	839	15	205			17,585	30	527,550
LIPOchip followed by CGA for negatives	11	287	713	15	79			21,695	30	650,850
Elucigene FH20 followed by LIPOchip followed by CGA for negatives	5	161	839	10	126	713	15	24,085	30	722,550
Elucigene FH20 followed by MLPA for negatives	5	161	839	2	45			6678	30	200,340
LIPOchip followed by MLPA for negatives	11	287	713	2	45			12,426	30	372,780
Elucigene FH20 followed by LIPOchip followed by MLPA for negatives	5	161	839	10	126	713	2	14,816	30	444,480

a The numbers of test-positives on the first test are calculated using the formula: number in cohort × sensitivity of test × prevalence + [(1 − specificity) × (1 − prevalence)].

b The number of test-positives on the second test depend on whether the second test is fully or only partially additive in the additional cases detected over and above the first test. The formula is as described in footnote 'a', but with some minor alterations to reflect the relationship between the sensitivities of the first and second tests. For full details of the calculation methods, see page 50, *Identification of probabilities for the decision model*.

c Total MOLUs are calculated as: (MOLU test 1 × number in cohort) + (MOLU test 2 × number receiving test 2). For example, total costs for Elucigene FH20 followed by CGA are calculated as [(1000 × 5) + (839 × 15)] = 5000 + 12,585 = 17,585 MOLUs. This is equivalent to 17,585 × 30 = £527,550 total diagnostic cost for a cohort of 1000 index patients receiving this testing strategy.

then the sample is sequenced for an additional €100. Therefore, assuming that the sensitivity of LIPOchip is the same regardless of where it is processed and using similar methodology to that in *Table 22*, we estimate the total cost of the strategy (before transportation of samples costs) as $(1000 \times 250 \times 0.89) + (713 \times 100 \times 0.89) = £285{,}957$.

The cost of targeted sequencing may also be estimated using the MOLU system. Targeted sequencing (including DNA extraction) is allocated a MOLU of 3. At a cost of £30 per MOLU, this would amount to £90 per targeted sequencing test. Based on the MOLU system, targeted sequencing is cheaper than Elucigene FH20 and is therefore the strategy of choice for cascading relatives.

Low-density lipoprotein cholesterol concentration measurements will be taken for all members of the study, regardless of testing strategy. Additional measures will, however, be carried out to confirm the diagnosis. Therefore, an additional two LDL-C tests will be required (at least one of which will be a fasting blood sample) to confirm the Simon Broome diagnosis if this is the method of diagnosis being adopted. It is assumed that, in order to get an extra blood test taken for the additional LDL-C measurement, an additional visit to a GP will be required. It is not expected that transportation costs of samples sent to laboratories for analysis will differ significantly between LDL-C and genetic tests as both require the transportation of potentially hazardous blood specimens.

Treatment costs

As discussed in *Treatment options to be evaluated* and as recommended by CG71,[1] treatment will be of either high or low intensity, predominantly with statins. Should a patient be intolerant to statins, treatment may be administered using ezetimibe as per the NICE CG71[1] guideline. There is, however, some debate as to the relative effectiveness of ezetimibe monotherapy; therefore, only a small proportion of patients are likely to receive this treatment in practice (Dr William Simpson, NHS Grampian, personal communication). Also based on personal communication (Dr Anthony Wierzbicki), ezetimibe as monotherapy is ineffective and patients who have an inadequate response to statins may need to be treated with ezetimibe plus bile acid sequestrants. A number of FH patients will receive polypharmacy incorporating treatment with statins and ezetimibe. *Table 23* details the unit costs per year of treatment with all of the potential drugs included in the modelling process with costs sourced from the *British National Formulary* (BNF).[76] To reflect differential treatment practice among clinicians, various combinations of these drugs (based on clinical expert opinions) are explored in the model. The most common combination therapies are included in *Table 23*.

For the base-case analysis, we used data from the FH audit 2010,[18] the most up-to-date data source on FH treatment in practice. We also use data from clinical experts (Dr Anthony Wierzbicki, Guy's and St Thomas' Hospitals NHS Trust, 2011, personal communication, and Dr William Simpson, NHS Grampian, personal communication) to conduct sensitivity analysis surrounding the proportions of patients on each treatment as part of either a high- or a low-intensity statin therapy. The cost impact of atorvastatin, which is due to come off patent during the course of this assessment, will have implications for treatment costs in the model. This will be explored in sensitivity analyses.

Costs of cardiovascular events avoided as a result of treatment

Table 24 details the costs of cardiovascular events avoided. For the base-case analysis, these costs have been calculated using weighted averages of all Health Resources Group (HRG) codes pertaining to each cardiovascular event avoided. Elective and non-elective tariffs from PBR data for 2010–11[74] are used and weighted for the numbers of elective and non-elective cases sourced from the Hospital Episodes Statistics online database (www.hesonline.nhs.uk/Ease/servlet/ContentServer?siteID=1937&categoryID=192).

Data sourced from current NICE guidelines[1] such as for subsequent MI are not available as part of PBR nor do any national tariff prices exist for these events. Therefore, values have been sourced from CG71[1] and inflated to current price levels for use in the model. Costs of cardiovascular death or other deaths have been assumed to be equal to £0 as it is not envisaged that this would have cost implications for the NHS. However, such deaths avoided would have great impact on the results from a societal perspective.

List of assumptions

A number of assumptions have been made throughout the modelling exercise and for the base-case model; the impact of each will be explored in relevant sensitivity analyses. *Table 25* summarises the main assumptions made throughout the health economic modelling process.

TABLE 23 Unit costs of drug treatments used in the economic modelling

Treatment strategy	Number of tablets per pack	Cost per pack (£)	Cost per year (£)	Source
Atorvastatin monotherapy 40 mg[a]	28	24.64	321.20	BNF 2011[76]
Atorvastatin monotherapy 80 mg[a]	28	28.21	367.74	BNF 2011[76]
Rosuvastatin monotherapy 10 mg	28	18.03	235.03	BNF 2011[76]
Rosuvastatin monotherapy 20 mg	28	26.02	339.19	BNF 2011[76]
Rosuvastatin monotherapy 40 mg	28	29.69	387.03	BNF 2011[76]
Simvastatin monotherapy 20 mg	28	1.01	13.17	BNF 2011[76]
Simvastatin monotherapy 40 mg	28	1.32	17.21	BNF 2011[76]
Simvastatin monotherapy 80 mg	28	2.29	29.85	BNF 2011[76]
Ezetimibe monotherapy	28	26.31	342.97	BNF 2011[76]
Rosuvastatin 20 mg + ezetimibe	28	52.33	682.16	BNF 2011[76]
Simvastatin 40 mg + ezetimibe	28	27.63	360.18	BNF 2011[76]
Atorvastatin 40 mg + ezetimibe[a]	28	50.95	664.17	BNF 2011[76]
Simvastatin 40 mg + ezetimibe	28	38.98	508.13	BNF 2011[76]

a Cost of atorvastatin based on current BNF pricing. Atorvastatin is likely to come off patent in 2011 and costs will mirror those of the simvastatin generic equivalent.

TABLE 24 Costs of cardiovascular events

Event	Cost (£)	Source
No event	74	NICE 2008[1]
MI (first year)	3780	Department of Health 2011[74]
MI (subsequent)	500	NICE 2008[1]
Stroke (first year)	4335	Department of Health 2011[74]
Stroke (subsequent)	2336	Department of Health 2011[74]
PAD (first year)	2212	Department of Health 2011[74]
PAD (subsequent)	285	NICE 2008[1]
Heart failure	4379	Department of Health 2011[74]
Heart failure (subsequent)	500	Assumption
Revascularisation	8610	Department of Health 2011[74]
Revascularisation (subsequent)	500	As MI (subsequent)
Unstable angina (first year)	2074	Department of Health 2011[74]
Unstable angina (subsequent)	500	As MI subsequent
Cardiovascular death	0	NICE 2008[1]
Death, other	0	NICE 2008[1]

TABLE 25 List of major assumptions, justification and method for dealing with associated uncertainty

Assumption	Justification for assumption	Additional comments
Cascade testing is of first-, second- and third-degree relatives of the index proband case	This is the widest spectrum of relatives recommended by NICE clinical guideline CG71[1] and is recommended if possible	Sensitivity analysis will explore cascade testing of first- and second-degree relatives only
The percentage of probands providing family history and agreeing for the initiation of contact with relatives is 60% and the proportion of relatives agreeing to be tested is 65%	Assumption based on NICE clinical guideline CG71[1]	Assumption will be adapted and varied in sensitivity analyses based on data from Hadfield and colleagues[67]
Cost of atorvastatin is based on BNF values	BNF	Cost of atorvastatin based on reduced pricing as a result of coming off patent will be explored in sensitivity analysis
10% of negative relatives receive low-intensity statin therapy	Relatives who are negative for FH are test-negative and are unlikely to require treatment (author assumption)	In sensitivity analysis a proportion of negatives will receive lipid-lowering therapy based on low-intensity statins (this will not assume costs of annual follow-up in secondary care). A range of 0–50% will be explored
No QALY decrements for patients testing false-positive for FH	Author assumption	Patients who test false-positive may incur a QALY decrement due to stress and anxiety associated with having a condition; however, if they have high LDL-C levels it is likely that this will be offset by the knowledge that they are being treated for their high cholesterol and will be at reduced risk of cardiovascular disease
Prevalence, sensitivities and specificities for cascade testing using LDL-C are assumed to be the same for cascade testing from index test-negatives and index test-positives	Author assumption	All index cases have a clinical diagnosis of FH regardless of whether or not they have a detectable mutation. Sensitivity analysis varies all estimates of test sensitivity and specificity in the model
All index cases will require treatment of some kind	As patients will be positive for FH, they will have elevated cholesterol levels by definition and will be at increased risk of cardiovascular events	Sensitivity analyses will assume a fraction of these patients are treated (i.e. only those with a genetically confirmed mutation)

Data analysis

Base-case analysis

For the base-case analysis, we analyse an index patient of age 50 years, with an assumed average first-degree relative age of 50 years. The decision model is run on the basis of a hypothetical cohort of 1000 patients with a clinical diagnosis of FH based on the Simon Broome criteria (including both definite FH and possible FH). Cost and QALY values are estimated as described in the preceding sections and applied to the number of people passing through each branch of the decision tree illustrated in *Figure 9*. On the basis of test accuracy, a proportion of all 1000 index patients are positive (true-positive or false-positive) or negative (true-negative or false-negative). These patients are assigned the relevant cost and QALY values as described and total costs and QALYs are generated for the full cohort.

Test strategies are ranked in ascending order of cost. Those strategies that are more costly and less effective are excluded on the basis of simple dominance. Additional tests that are dominated by a combination or two or more alternative strategies are excluded by extended dominance. ICERs are calculated as incremental costs divided by incremental QALYs between non-dominated strategies. This is the most common method of presenting ICERs and relates the options sequentially ranked by costs. For the purposes of this assessment, the most relevant comparators are:

1. CGA, recommended indirectly by NICE guidance CG71.[1]

2. LDL-C concentration measurement only. The reason for this is that, in practice, LDL-C is the main method of identification presently adopted in the UK (although genetic testing is more common in Scotland, Wales and Northern Ireland than in England).

Therefore, ICERs are presented as cost per QALY compared with the two suggested reference standards for this evaluation (LDL-C and CGA).

This process is applied to two distinct research questions. First, we investigate the cost-effectiveness of each of the 12 strategies for index cases alone. However, of greater importance and thus the primary focus of the analysis is to present cost-effectiveness estimates for the complete process of index case confirmation of clinical diagnosis but also for the identification and testing of relatives (i.e. the whole cascade testing process).

Subgroup and additional scenario analysis

The cost and QALY results for different age groups are explored in this section for the full cascading project only (i.e. index and relative cases). Results for index cases alone are presented in *Appendix 12*.

These subgroup analyses include a range of age profiles and also include the incorporation of any available evidence relating to the efficacy of statins in the treatment of children. To this end, we have completed a structured search of the literature, which has identified four systematic reviews of the efficacy of statins in children, the most recent of which is a Cochrane review of high quality that is used to inform the discussion and the model.[77] The data suggest that statins are efficacious in children in reducing cholesterol and have non-significantly different adverse events to placebo. Therefore, statins are likely to be safe in children with FH although long-term follow-up of this patient group is required. As data relating directly to CHD are lacking, treatment effect relative to CHD is assumed to be similar to that of a young adult (equivalent to a 30-year old index case in the economic model).

A number of age-specific subgroups were considered (probands aged 15, 30, 50, 65, 75 and 85 years). These age subgroups are similar to those used in previous economic modelling for FH[1] and represent a good distribution of the ages of the population who may present for testing. *Table 26* details the calculated number of relatives for each index case and their average age used in the model.

As discussed in *Model structure*, there may be alternative estimates of cost-effectiveness based on whether the index case is identified as definite FH or possible FH as their clinical diagnosis. It should be noted, however, that because of a lack of sensitivity data for each test separated into definite FH and possible FH subgroups, it was not possible to conduct robust analyses of FH cases split by clinical diagnosis subgroup. We have, however, conducted threshold analyses which

TABLE 26 Details of index case age and associated number and age of relatives

Age of index case years	Number of first-degree relatives	Number of second-degree relatives	Number of third-degree relatives	Average age of all relatives years
15	3	6	8	50
30	5	4	4	30
50	5	4	4	50
65	3	6	8	30
75	3	6	8	50
85	2	6	4	30

show the combination of mutation prevalence and test sensitivity that would be required for the candidate test to be considered cost-effective as a pre-screen to CGA. The probabilistic sensitivity analysis accounts for the combined variation in all of the input parameters.

Sensitivity analyses

As many assumptions are made throughout the modelling process and selective data are chosen to inform the parameters, it is possible that the results generated will be sensitive to some of the judgement calls, assumptions and decisions made in the analysis. Therefore, we carry out a range of sensitivity analyses to determine the sensitivity of the base-case results to changes in our assumptions. A range of univariant deterministic analyses are presented in *Appendix 14*, the main results of which are reported and discussed in *Analysis of uncertainty, including probabilistic sensitivity analysis*. In addition, a probabilistic sensitivity analysis is also presented to explore uncertainty in the model.

Areas of uncertainty that are explored include:

1. Prevalence rates of FH-causing mutations among clinically diagnosed index cases and at-risk relatives.
2. Treatment differences for those with genetically confirmed FH and those without a genetic confirmation. The implication of forthcoming price reductions of atorvastatin is also explored.
3. Uncertainty surrounding the proportion of probands and relatives with a given test result receiving treatment (e.g. the proportion of those with a false-negative or true-negative test result receiving statin therapy).
4. The costs of diagnostic strategies, especially issues of uncertainty surrounding the MOLU pricing system and the likely cost of a 1-unit MOLU output.
5. Key assumptions relating to the model structure, including cascade testing only of first- and second-degree relatives, discount rates applied to costs and effects, the impact of not cascade testing negative index cases and the proportion of index and relative cases agreeing to participate in the identification and testing process.
6. Uncertainty associated with assumptions listed in *Table 25* including structural assumptions regarding management of negative-testing index and relative cases.

Probabilistic sensitivity analysis

Deterministic one-way sensitivity analyses and point estimates of ICERs do not adequately provide information on the true impact of uncertainty surrounding the model parameters. Because of imperfect information on both the resource use and effectiveness of each treatment strategy, costs and QALYs are highly likely to be subject to at least some degree of uncertainty. Therefore, we conducted additional probabilistic sensitivity analysis using Monte Carlo simulation (5000 repetitions). Distributions were fitted to each of the parameters based on published studies (where available), CG71 data[1] and a number of assumptions where no data were available. For example, where insufficient data existed in published sources to fit distributions to parameters, standard errors were assumed in order to calculate alpha and beta values. This may slightly under- or overestimate the variation in some of the parameters; however, it is not likely to impact greatly on resultant cost-effectiveness acceptability curves (CEACs). For sensitivity of test strategies (Elucigene FH20 and LIPOchip) the analysis was bounded by the highest and lowest reported mean values in all of the studies identified from the systematic review of the literature. Full details of probabilistic sensitivity analysis parameters are presented in *Appendix 16*.

The net benefit framework was used to estimate net monetary benefits for each simulation as described in Briggs.[78] The defining characteristic of this approach is that all strategies add

to a probability of cost-effectiveness equal to 1. This uncertainty is illustrated in the form of CEACs for each of the non-dominated strategies of testing. CEACs for the base-case analysis are presented in the text, with supplementary analyses following the same approach for each age subgroup in the model presented in *Appendix 15* for completeness. The analysis is presented for non-dominated test strategies only. The comparison for the calculation of incremental costs and QALYs for this analysis is LDL-C as this is current practice in the NHS. As the remit of this report is primarily to assess the cost-effectiveness for index cases and relatives, we have not conducted probabilistic sensitivity analysis for index cases alone. In addition, CEACs are presented for 5%, 10%, 20% and 50% mutation prevalence rates in order to reflect the uncertainty surrounding mutation detection rates in various subgroups of the population, primarily varying based on ethnic background.

Results of economic analysis

Results presented for the base-case analysis are subject to the assumptions listed in *Table 25*.

Summary of test results for a hypothetical cohort of 1000 familial hypercholesterolaemia patients

Table 27 details the flow of a hypothetical cohort of 1000 patients through the model based on those testing false-positive, true-positive, false-negative and true-negative. The values for sensitivity and specificity are combined values for all definite FH or possible FH patients based

TABLE 27 Test results for a hypothetical cohort of 1000 patients by testing strategy for index cases and cascading of both test-positive and test-negative relatives[a]

	Index cases					Relatives of positive index cases (tested using targeted sequencing)[b]					Relatives of negative index cases (tested using LDL-C)[b]				
Diagnostic test	TP	FP	TN	FN	Total	TP	FP	TN	FN	Total	TP	FP	TN	FN	Total
Elucigene FH20	161	0	635	205	1000	374	0	374	0	748	900	255	1307	662	3124
Elucigene FH20_LIPOchip	287	0	635	79	1000	667	0	667	0	1335	765	216	1111	563	2655
Elucigene FH20_CGA	365	0	635	0	1000	851	0	851	0	1701	680	193	989	501	2362
Elucigene FH20_LIPOchip_CGA	365	0	635	0	1000	851	0	851	0	1701	680	193	989	501	2362
Elucigene FH20_MLPA	205	0	635	160	1000	478	0	478	0	956	852	241	1238	627	2958
Elucigene FH20_LIPOchip_MLPA	331	0	635	34	1000	772	0	772	0	1543	717	203	1042	528	2489
LIPOchip	287	0	635	79	1000	667	0	667	0	1335	765	216	1111	563	2655
LIPOchip platform (Spain)	321	0	635	45	1000	747	0	747	0	1493	728	206	1058	536	2529
LIPOchip_CGA	365	0	635	0	1000	851	0	851	0	1701	680	193	989	501	2362
LIPOchip_MLPA	331	0	635	34	1000	772	0	772	0	1543	717	203	1042	528	2489
CGA	365	0	635	0	1000	851	0	851	0	1701	680	193	989	501	2362
LDL-C	329	451	184	37	1000	835	236	1214	615	2901	236	67	344	174	821

FN, false-negative; FP, false-positive; TN, true-negative; TP, true-positive.

a Numbers are rounded to the nearest whole person.

b Cascaded numbers include assumptions in relation to number of first-degree relatives, number of subrelatives, percentage of indexes providing family pedigree information, and percentage of relatives responding to contact and agreeing to cascade testing as well as prevalence rates among tested relatives.

on the Simon Broome criteria. We have used estimates of sensitivity and specificity derived from the clinical effectiveness review and applied these to the model as discussed in *Methods for economic analysis*.

Assumptions relating to the incidence of FH among the tested population are discussed in *Model structure*; however, for the base-case model we assume a mutation detection rate of 36.5%[37] among people who are either possible or definite FH using the Simon Broome clinical diagnosis (i.e. approximately one in three reporting for testing will test positive based on CGA). Sensitivity analysis explores the variation in this estimate.

As we have assumed that each genetic test is associated with specificity equal to 1, there are no false-positives for the base-case analysis. However, data suggest that LDL-C among index cases has a specificity of 0.29,[44] indicating that a substantial number of positive test results will in fact be false-positives.

Mean cost and mean treatment effects associated with each diagnostic strategy

Index (proband) familial hypercholesterolaemia patients

Table 28 presents total costs and total QALYs for each treatment strategy for index cases alone ranked according to cost with dominance or otherwise indicated. Patients without FH will have a slightly longer survival prognosis and will thus receive slightly greater QALY gains than those with FH. Such patients are clinically diagnosed as having FH, have high lipid levels and are at an increased risk of CHD and so will have a positive response to cholesterol-lowering therapy.

The Elucigene FH20 diagnostic strategy alone generates the lowest costs for identifying index patients for two reasons: first, it is the cheapest genetic diagnostic test available and, second, it detects the lowest number of true-positive index cases. Therefore, it confirms the clinical diagnosis in the fewest index cases with FH and for that reason is associated with the lowest QALYs of all of the tests included. LDL-C identifies the largest proportion of positives (not necessarily true-positives for FH – although all index cases are technically true-positives based on their clinical diagnosis) and has the highest QALY gain as it detects the greatest number of patients at increased risk of CHD. Of the non-dominated sequences, LIPOchip platform (Spain) and CGA are both associated with ICERs between £20,000 and £35,000 per QALY gained.

TABLE 28 Total costs, total QALYs and sequentially presented ICERs for the identification of index cases

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	14,192,370	13,005			
Elucigene FH20_MLPA	14,462,441	13,016	Ext Dom	Ext Dom	Ext Dom
LIPOchip	14,991,529	13,037	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	15,063,229	13,037	Dominated	Dominated	Dominated
LIPOchip platform (Spain)	15,154,374	13,045	962,004	40	24,025
LIPOchip_MLPA	15,254,040	13,048	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	15,325,740	13,048	Dominated	Dominated	Dominated
CGA	15,528,212	13,056	373,838	11	33,402
Elucigene FH20_CGA	15,575,762	13,056	Dominated	Dominated	Dominated
LIPOchip_CGA	15,699,062	13,056	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	15,770,762	13,056	Dominated	Dominated	Dominated
LDL-C	17,678,183	13,079	2,149,970	23	93,518

Ext Dom, extendedly dominated.
Costs and Incremental costs are rounded to the nearest whole pounds sterling. QALYs and incremental QALYs are rounded to the nearest whole QALY. ICERs are also rounded to the nearest £/QALY gained from the economic model.

Index cases and relatives

However, where genetic testing has the greatest advantage over LDL-C is in the identification of relatives for cascade testing. Cascade testing using LDL-C alone is less likely to be cost-effective in this population because of the large number of false-positives (including relatives incorrectly identified as having FH) who may be treated using high-intensity statin therapy when low-intensity therapy would have sufficed to reduce their cholesterol levels. Assumptions regarding false-positive relatives are detailed in *Table 25* and can be tested in sensitivity analysis within the model. *Table 29* presents total costs and QALYs for index and relative cases combined (i.e. a whole integrated strategy for the identification and management of index cases and relatives with FH). Cascade testing of relatives of an index case with an identified mutation is by targeted sequencing. This is because targeted sequencing is less costly than both of the other candidate tests. Therefore, as all tests would detect the identified mutation they are supposed to in the relatives, targeted sequencing is the most cost-effective way to do this in relatives of a mutation-positive index case.

In the analysis presented in *Table 29*, LDL-C is the least effective of all tests. Elucigene FH20 is the least costly genetic testing strategy and is also the most cost-effective of all non-dominated genetic testing strategies relative to LDL-C, being less costly, more effective and thus dominant. CGA is the most effective non-dominated strategy in terms of QALYs gained, with an associated ICER of £2135 per QALY gained relative to the next most effective non-dominated strategy (LIPOchip platform, Spain). Combination genetic tests are dominated by single genetic test strategies. For example, Elucigene FH20 followed by LIPOchip is dominated by LIPOchip alone-meaning that the extra cost of pretesting with Elucigene FH20 does not add any additional QALYs over and above LIPOchip. The reason for this is that LIPOchip will detect the same mutations and cost more when added to Elucigene FH20. A similar argument can be made for tests used for pre-screening prior to CGA. The case for test strategies including MLPA as a component is slightly different in that MLPA detects deletions and duplications of the gene and so detects approximately an extra 5% of mutations that would not otherwise be detected by Elucigene FH20. MLPA is incorporated and included in the CGA process and has not been considered separately here. In relation to LIPOchip, there is some uncertainty in relation to

TABLE 29 Total cost and QALY implications for index and relative cases[a]

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	43,371,985	36,653			
LDL-C	43,880,789	34,744	Dominated	Dominated	Dominated
Elucigene FH20_MLPA	44,470,770	37,216	Ext Dom	Ext Dom	Ext Dom
LIPOchip	46,506,304	38,240	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	46,578,004	38,240	Dominated	Dominated	Dominated
LIPOchip platform (Spain)	47,298,810	38,668	3,926,825	2015	1949
LIPOchip_MLPA	47,597,529	38,803	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	47,669,229	38,803	Dominated	Dominated	Dominated
CGA	48,501,362	39,231	1,202,552	563	2135
Elucigene FH20_CGA	48,548,912	39,231	Dominated	Dominated	Dominated
LIPOchip_CGA	48,672,212	39,231	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	48,743,912	39,231	Dominated	Dominated	Dominated

Ext Dom, extendedly dominated.

a Note that cascade testing from negative index cases is undertaken using LDL-C; cascade testing of positive LDL-C index cases is also undertaken using LDL-C.

Costs and Incremental costs are rounded to the nearest whole pounds sterling. QALYs and incremental QALYs are rounded to the nearest whole QALY. ICERs are also rounded to the nearest £/QALY gained from the economic model.

the detection of deletions and duplications of the gene. Therefore, we have taken a pragmatic approach and included LIPOchip alone and LIPOchip followed by MLPA. This will allow the reader to decide, based on further investigation of LIPOchip, whether or not MLPA would be required to obtain a definitive diagnosis among positive test results (i.e. a specificity of 1) as assumed in the model.

Incremental analysis for reference case and other scenarios

Index cases

Tables 30 and *31* evaluate the non-dominated sequences compared with the relevant comparators for index cases. The scope and protocol for this assessment define two important comparators: (1) the comparator recommended as part of the NICE clinical guidelines – full genetic DNA testing (or CGA as defined in our protocol) and (2) LDL-C, which is currently the most commonly used method as part of the Simon Broome criteria to identify FH in practice in the UK. Currently, DNA testing is available only in 15% of UK primary care trusts (UK FH audit project 2010[18]) and therefore LDL-C is deemed an appropriate comparator based on current clinical practice in the UK (NICE diagnostic advisory group, 2011, personal communication).

Of the non-dominated sequences, LDL-C is the most costly and most effective test overall (see *Table 30*). Elucigene FH20 is the least costly but also the least effective test in terms of QALYs. In fact, all of the non-dominated testing strategies are cheaper overall and generate fewer QALYs than LDL-C. Although diagnosis costs for LDL-C are lower than the alternatives presented, treatment costs are much higher. This is because as all index patients will technically have FH based on their clinical diagnosis on the Simon Broome criteria, they will benefit from statin therapy. Additionally, even if they were not true FH, they would still be at an increased risk of coronary artery disease based on their cholesterol levels and so would benefit from treatment. LDL-C is therefore also associated with the greatest number of QALYs gained for index cases. This is because, should a negative diagnosis be based on a genetic test, patients who test false-negative may be inappropriately treated and would thus gain fewer QALYs than if they were prescribed high-intensity treatment for their FH based on LDL-C levels.

TABLE 30 Comparison of non-dominated sequences vs LDL-C (index cases only)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
Elucigene FH20	14,192,370	13,005	–3,485,812	–74
LIPOchip platform (Spain)	15,154,374	13,045	–2,523,808	–34
CGA	15,528,212	13,056	–2,149,970	–23
LDL-C	**17,678,183**	**13,079**		

Costs and Incremental costs are rounded to the nearest whole pounds sterling. QALYs and incremental QALYs are rounded to the nearest whole QALY.

TABLE 31 Comparison of non-dominated sequences vs CGA (index cases only)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	14,192,370	13,005	–1,335,842	–51	
LIPOchip platform (Spain)	15,154,374	13,045	–373,838	–11	
CGA	**15,528,212**	**13,056**			
LDL-C	17,678,183	13,079	2,149,970	23	93,518

Costs and Incremental costs are rounded to the nearest whole pounds sterling. QALYs and incremental QALYs are rounded to the nearest whole QALY. ICERs are also rounded to the nearest £/QALY gained from the economic model.

Table 31 presents similar information for index cases alone when the comparator of interest is CGA.

When the comparison of interest for index cases alone is CGA, all other non-dominated genetic tests are less costly and less effective than CGA. The question for a decision-maker in this scenario would thus be whether or not the cost savings are worth the associated QALY loss. ICERs are not reported in informing such a question as there is lack of evidence regarding how much society is willing to accept in compensation (in the form of cost savings) for a QALY loss.

Figure 10 presents the cost-effectiveness plane comparing all tests for index cases. This confirms the results alluded to in the tables of results above.

There are two important things to note from this illustration. First, LDL-C is the most costly strategy (driven by high-intensity statin treatment costs). As all patients are at risk of cardiovascular disease, however, QALY gain is highest driven by the extra-intensive treatment based on false-positive diagnoses of FH by LDL-C. These patients benefit from the increased statin therapy as they are at increased risk of cardiovascular disease based on their cholesterol levels. Second, the graph illustrates the dominance of single test strategies over similar strategies preceded by less-sensitive screening tests such as Elucigene FH20. As all strategies ending in CGA generate the same QALY gains, dominance is due to greater costs amongst multiple test strategies.

Confirmation of clinical diagnosis in index cases and cascade testing of relatives

Tables 32 and *33* evaluate the non-dominated sequences compared with the relevant comparators for the full process of index case confirmation of the clinical diagnosis and cascade testing of relatives. The comparators are LDL-C and CGA as in the preceding section.

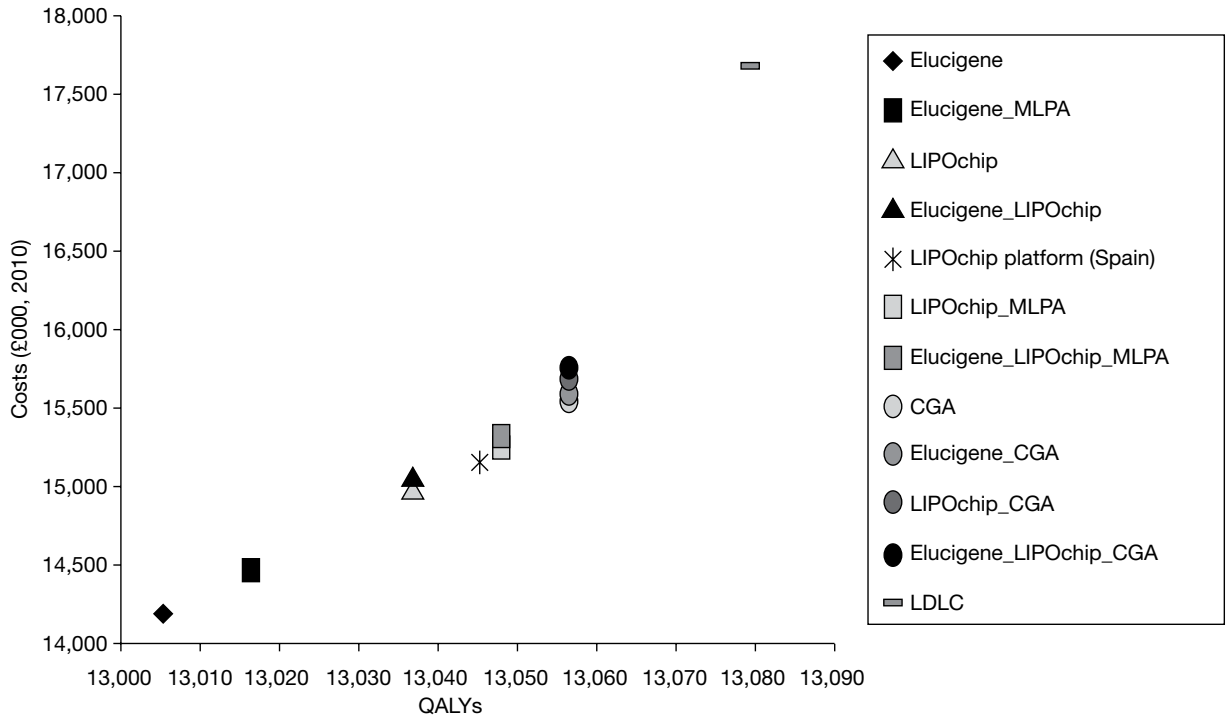

FIGURE 10 Cost-effectiveness plane (index cases).

TABLE 32 Comparison of non-dominated sequences vs LDL-C (identification of index cases and cascade testing of relatives)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	43,371,985	36,653	–508,805	1909	**Dominant**
LDL-C	**43,880,789**	**34,744**			
LIPOchip platform (Spain)	47,298,810	38,668	3,418,020	3924	**871**
CGA	48,501,362	39,231	4,620,573	4487	**1030**

Costs and Incremental costs are rounded to the nearest whole pounds sterling. QALYs and incremental QALYs are rounded to the nearest whole QALY. ICERs are also rounded to the nearest £/QALY gained from the economic model.

TABLE 33 Comparison of non-dominated sequences vs CGA (identification of index cases and cascade testing of relatives)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
Elucigene FH20	43,371,985	36,653	–5,129,377	–2578
LIPOchip platform (Spain)	47,298,810	38,668	–1,202,552	–563
CGA	**48,501,362**	**39,231**		

Costs and Incremental costs are rounded to the nearest whole pounds sterling. QALYs and incremental QALYs are rounded to the nearest whole QALY.

Multiple testing strategies are dominated by single testing strategies generating the same sensitivity and test-positive rate overall. All non-dominated genetic tests are highly cost-effective compared with LDL-C in the identification of index cases with FH and cascade testing of relatives (assuming that society's willingness to pay for a QALY gain is £20,000). The Elucigene FH20 single test strategy is the most cost-effective, being less costly and more effective and thus dominant over LDL-C (see *Table 32*). However, should a decision-maker wish to have a DNA test with a definitive genetic diagnosis, (i.e. CGA) then this is more expensive but generates the most QALYs gained compared with LDL-C. Relative to LDL-C (current practice), CGA could be considered a cost-effective testing strategy with an associated ICER of only £1030 per QALY gained. This is also well below a willingness-to-pay value of £20,000 per QALY gained.

When cost and QALY pairs are compared with CGA (current NICE recommendations) for the whole process of identification of index cases and cascade testing of relatives, all non-dominated tests are less costly and less effective than CGA. *Table 33* presents this comparison.

Again, as discussed previously, the reporting of ICERs for this scenario does not inform the question of what reduction in QALYs a decision-maker is willing to accept in order to achieve a predefined cost saving. All non-dominated testing strategies are less costly and also less effective than CGA.

Figure 11 presents the cost-effectiveness plane comparing all tests for index cases and cascade testing of first-, second- and third-degree biological relatives. This confirms the results alluded to in the tables of results above.

In this scenario (including cascade testing of relatives in the analysis), LDL-C used as a method of identification of relatives is less costly than all other tests (with the exception of Elucigene FH20) but does not generate the same QALY gains as any of the genetics-based tests. LDL-C is an inexpensive test to carry out (relative to other more costly genetic options); however, LDL-C alone will falsely diagnose many index cases as having FH and hence many relatives will be

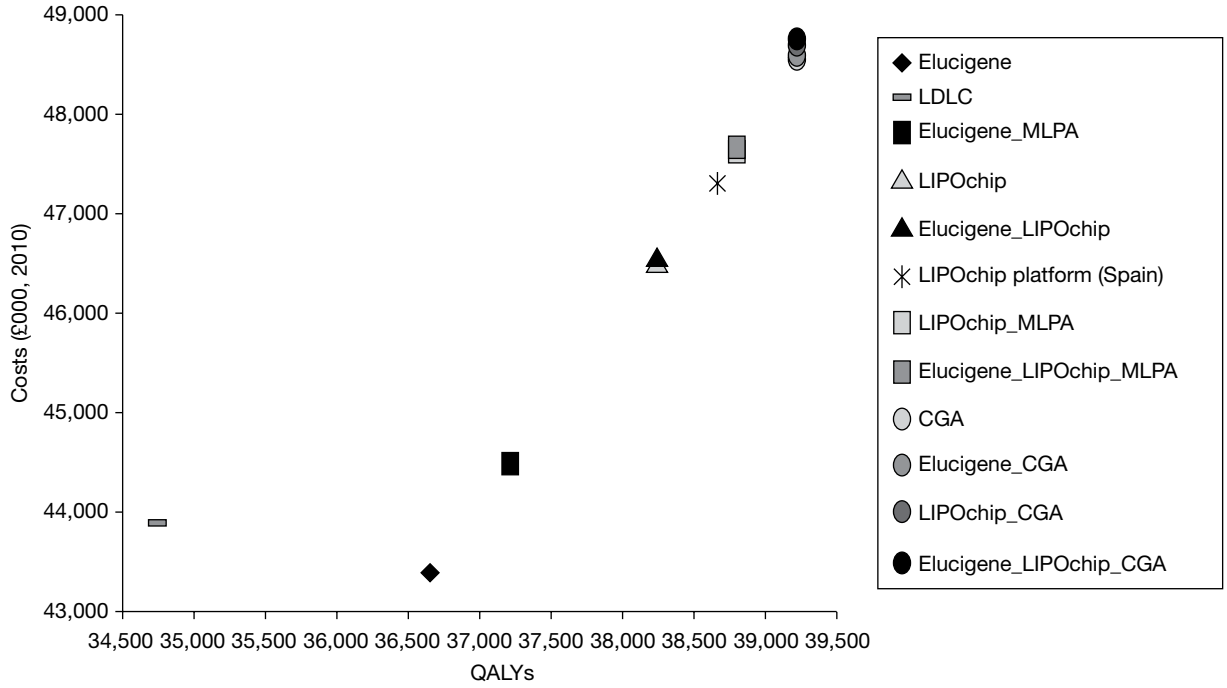

FIGURE 11 Cost-effectiveness plane for index cases and cascade testing of relatives.

cascade tested unnecessarily for fewer QALYs gained. LDL-C is thus dominated by the lower-cost Elucigene FH20 test.

Differential results for subgroups

The impact of varying the age of the index case and associated average age of relatives is explored in this section. As with the base-case analysis, results are presented sequentially and also incrementally relative to LDL-C and CGA. Analyses for index cases only are presented in *Appendix 12*.

For index cases alone, the results are quite difficult to interpret and there appears to be much variability in the ICERs depending on age (see results tables in *Appendix 12*). As in all other analyses, all pre-screen tests are dominated by more effective tests that generate cost savings due to treatment effects. For all index case ages, non-dominated test strategies appear to be less costly and less effective than LDL-C, with the exception of an 85-year-old index case, for which genetic tests are dominant over LDL-C. These results should, however, be interpreted with caution. The wide variability in the presented ICERs is due to small or indeed negligible QALY differences between strategies. This is because, for index cases alone, most if not all patients will be at risk of cardiovascular events and all will have a clinical diagnosis of FH.

Genetic testing has the advantage in the identification and treatment of relatives through the cascade testing process for all age subgroups and this is evident from associated tables (for index cases and relatives combined) reported in *Appendix 13* and discussed in the following paragraph.

The results presented suggest that, as in the base case, all pre-screening strategies are dominated by single test strategies detecting the same number of people, regardless of age. The reason for this is that costs associated with savings on test-positive cases are offset by submitting a whole cohort of negative patients through two or maybe three tests. As only a proportion will have a genetic mutation, these additional costs outweigh cost savings from those tested positive on

pre-screens such as Elucigene FH20 or LIPOchip. This confirms the base-case results presented in *Tables 29*, *32* and *33*. As reported for the base case in *Table 29*, relative to LDL-C, Elucigene FH20 is the most cost-effective option for all age groups analysed, with all ICERs under £1400 per QALY gained. This probably represents a highly cost-effective use of NHS resources. The next most cost-effective testing options after Elucigene FH20 are LIPOchip (platform processed in Spain), for which the costs per QALY gained are between £714 and £2513 irrespective of age group analysed, and CGA, with ICERs only slightly higher than those of LIPOchip (platform processed in Spain). Therefore, as in the base case, there are a number of tests that could be deemed cost-effective, all with very low ICERs relative to LDL-C. As discussed, should we wish to achieve a definitive diagnosis and generate the greatest QALY gain then CGA is a cost-effective means to achieve such an objective.

Summarising these results together, all of the age group analyses are consistent with the conclusions of the base-case analysis for an index case aged 50 years. Therefore, one may conclude that the conclusions of the model for index and relative cases are not sensitive to the age of the index case or associated relatives. CEACs based on probabilistic sensitivity analysis of the age subgroup results show some uncertainty at low threshold values of willingness to pay but, at threshold values > £5000 per QALY gained, CGA is the most likely cost-effective testing strategy, increasing to almost 100% as the threshold value increases towards a threshold ceiling ratio of £20,000 per QALY gained. CEACs reporting these results are presented for illustration in *Appendix 15*.

Because of a lack of good-quality data differentiating the sensitivities of the tests for definite and possible FH, we have conducted a threshold analysis indicating the prevalence and sensitivity that would be required for the candidate tests to be cost-effective as a pre-screen for CGA. Additional sensitivity analysis around the maximum and minimum values of all reported studies is presented in the following section. At the current estimate of sensitivity of Elucigene FH20, there would need to be an underlying prevalence of mutations of 61% at current prices of CGA. Should the price of CGA drop in the future as a result of next-generation sequencing, the required prevalence of underlying mutations would need to be 93%. This is based on an assumed price reduction of 40% in the cost of DNA sequencing in the future. The results for LIPOchip are less favourable at current levels of sensitivity as the lower cost of Elucigene FH20 followed by CGA would dominate LIPOchip followed by CGA at high prevalence rates, irrespective of whether or not we apply a cost reduction of 40% to DNA sequencing as part of CGA.

From an alternative perspective, one may be interested in the sensitivity of Elucigene FH20 and/or LIPOchip that would be required to generate cost savings as a pre-screen to CGA at current levels of mutation prevalence. Elucigene FH20 would be required to have a sensitivity of at least 73% to be a cost-saving pre-screen to CGA for a mutation prevalence rate of 36.5% as used in the base-case economic model. LIPOchip would not be cost-effective as a pre-screen to CGA for any plausible sensitivity values at this mutation prevalence level. Plausible values are defined as those sensitivities below the sensitivity of CGA. The reason for this is that, because of the relatively low prevalence of mutations, even at a sensitivity of 90%, only 33% of cases would be positive, with the remaining 67% requiring CGA to confirm the presence or otherwise of a FH-causing genetic mutation.

Therefore, if the goal is to gain an unequivocal diagnosis, for low mutation prevalence rates, pre-screening with Elucigene FH20 or LIPOchip prior to CGA is not cost-effective. At high prevalence rates, > 61%, Elucigene FH20 may offer a cost-effective option; however, this is less likely once the costs of next-generation sequencing fall.

Analysis of uncertainty, including probabilistic sensitivity analysis

One-way deterministic sensitivity analyses

A range of one-way deterministic analyses are presented to investigate the sensitivity of the model to uncertainty in some of the key parameters and in relation to model structural assumptions as outlined in *Table 25*. All deterministic sensitivity analyses were carried out on the base case of an age 50 years index case.

A full range of sensitivity analyses in relation to treatment effect have been carried out previously in the NICE clinical guidance CG71.[1] The model was found to be insensitive to a range of sensitivity analyses including assumptions surrounding nurse and consultant time with patients, costs of cholesterol testing, costs of letters to relatives for cascading, cascading from alternative numbers of relatives (first and second degree), relative risks of non-cardiovascular disease deaths and treatment effect used in the model. As data from the CG71[1] assessment have been updated and used for the purposes of this report, it is highly unlikely that these sensitivity analyses will have any impact on the sequences of ICERs for this analysis. We have additionally explored the impact of including a cost of £80 (standard A&E tariff) for those patients who die in the model. This is to reflect any additional costs that may be involved over the £0 assumed in the base-case analysis. The results are not sensitive to this assumed value.

Therefore, the focus of sensitivity analyses for this assessment centres on parameters and assumptions that we hypothesise may have an impact on the sequence of ICERs or on the overall cost-effectiveness conclusions. Many parameters alter the cost-effectiveness of identifying index cases alone; however, as the remit for this report is primarily the detection and treatment of relatives with FH, we focus mainly on analyses that affect the overall outcome (i.e. the confirmation of index cases and the cascade testing of at-risk relatives). Full analyses for both groups are included in *Appendix 14* for information. In the appendix, results for the index case analysis are presented first, followed by results for index cases and relatives together. The order of tables follows the sequence of results presented below.

The following discussion refers to index cases and relatives together.

Prevalence of familial hypercholesterolaemia-causing mutations among index cases and relatives

Prevalence of FH-causing mutations among index cases is varied between 28%[79] and 52%.[41] For both low and high estimates of mutation prevalence, the order of the ICERs remains unchanged compared with the base case. Elucigene FH20 remains the most cost-effective strategy relative to LDL-C (associated ICERs = dominant and £395 per QALY gained for low and high estimates respectively). The next most cost-effective options after Elucigene FH20 are LIPOchip (platform processed in Spain) and CGA for both low and high mutation prevalence rates with all ICERs < £1300 per QALY gained. See *Differential results for subgroups* for a threshold analysis estimating the prevalence required for Elucigene FH20 or LIPOchip to be deemed a cost-effective pre-screen to CGA.

Prevalence of FH-causing mutations among relatives of index cases is an uncertain parameter that is generally held to be approximately 50%, based on the logic that one out of every two offspring will inherit a genetic mutation. Sensitivity analysis varied this assumption by ±20% to between 40% and 60% of first-degree relatives inheriting the culprit gene (author assumption). A low estimate suggests that Elucigene FH20 is dominant, being less costly and generating more QALYs than LDL-C. After that, as in the base-case analysis, LIPOchip platform (processed in Spain) and CGA remain the next most cost-effective testing strategies. A higher estimate of mutation prevalence among relatives of 60% suggests the same three non-dominated test strategies as in the base case, all with ICERs of < £1200 per QALY gained. Therefore, as similar

tests are recommended as being cost-effective for all prevalence values considered, the base-case conclusions remain insensitive to any assumptions surrounding prevalence rates in either index cases or relatives with all ICERs for non-dominated strategies < £1300 per QALY gained relative to LDL-C.

Familial hypercholesterolaemia treatment

Analyses reducing the cost of atorvastatin did not change the base-case conclusions, with no difference in the sequence of the presented ICERs. Elucigene FH20 remains the most cost-effective option relative to LDL-C; LIPOchip (platform processed in Spain) is the next most cost-effective option followed by CGA, as was reported in the base-case analysis. ICERs for all three non-dominated tests are insensitive to changes in the cost of treatment used in the model (all reported ICERs are < £1100 per QALY gained relative to LDL-C).

Data in relation to the base-case model sourced treatment proportions for FH from the FH audit 2010[18] and assumed generic simvastatin treatment for those without confirmed FH. This assumption was tested using treatment proportions provided by Dr Anthony Wierzbicki (personal communication, Guy's and St Thomas' Hospitals NHS Trust, 2011). This assumed that both genetically confirmed FH and genetically non-confirmed FH patients would receive a range of treatments. This included polypharmacy for some patients including treatment with ezetimibe as well as statins. The order and magnitude of the ICERs relative to LDL-C remain similar to that in the base-case analysis.

The conclusions drawn are therefore not sensitive to changes in treatment pattern or to costs of treatment administered to patients.

The impact of the decision to treat negative-testing relatives or index cases

The base-case analysis assumes that 10% of negative-testing relatives will require treatment. However, it may be that 0% or at least no more than in the general population will require treatment. Therefore, sensitivity analysis investigates a scenario in which none of these relatives would receive statin therapy. In this scenario, the magnitude and order of the ICERs are very similar to those in the base-case analysis, with Elucigene FH20 remaining the most cost-effective strategy, dominating LDL-C. LIPOchip (platform processed in Spain) and CGA are the next most cost-effective options (ICERs of £902 and £1062 per QALY gained, respectively, relative to LDL-C). Hypothetically increasing this proportion to 50% does not lead to any significant change in the order or magnitude of the ICERs presented.

In an unlikely situation that negative index cases do not receive treatment or clinical follow-up, Elucigene FH20 is the only non-dominated genetic testing strategy and is less costly but less effective than LDL-C, the reason being that index cases testing negative for a FH-causing genetic mutation are still at significant risk of cardiovascular events and so not treating based on genetic mutation alone would lead to large numbers of at-risk individuals being missed, hence the reason LDL-C would be the most cost-effective strategy. It is important to note, however, that the above-mentioned analysis is for illustration only and is not necessarily a reflection of the true care pathway.

Costs of diagnostic strategies

Increasing or decreasing the MOLU costs associated with each test by ±£10 (varying cost per MOLU from £20 to £40) does not impact on the overall test order, with only minimal changes in the relevant ICERs. This is because the model is determined primarily around lifelong costs and health outcomes associated with treatment for FH or otherwise.

Sensitivity of key assumptions (model structure)

The assumption that cascade testing takes place of first-, second- and third-degree biological relatives of the index case is tested by assuming that the process stops after the second-degree relative regardless of test result. All genetic tests are even more cost-effective in this scenario. Elucigene FH20 is less costly and generates greater QALYs than LDL-C and is thus dominant. LIPOchip (Spain) and CGA are both associated with ICERs of < £800 per QALY gained.

The base-case analysis assumes that all index patients with a clinical diagnosis will have their family pedigree investigated, with cascade testing using targeted sequencing for relatives of genetically confirmed index cases. However, those that do not receive a genetic test or are test-negative will still be cascade tested using LDL-C. This is because, although a genetic mutation may not be detected, it is possible that such individuals have mutations or genes that have not yet been identified as causing FH. However, as a sensitivity analysis, we have explored the impact on the results of not cascade testing from such genetically test-negative index cases. In this scenario, all non-dominated genetic tests are actually less costly and less effective than LDL-C testing. Although the results are sensitive to this aspect of the model, clinical advice suggests that this would be highly unlikely in practice as cascade testing from negative index cases is a very important part of the cascade process. The results are not sensitive to assumptions regarding the proportion of index and/or relatives agreeing to have their family history investigated or agreeing for cascade testing to take place.

We varied the discount rate between 0% and 6% for costs and benefits as is standard practice in economic modelling to test our model to assumptions regarding uncertainty surrounding the value of future costs and health gains accrued over a lifetime horizon. For a discount of both 0% and 6% the order of the ICERs relative to LDL-C remained the same as in the base-case analysis. The magnitude of these ICERs showed no significant changes either. The results for the base-case analysis present estimates of cost-effectiveness based on current costs of CGA. However, the cost of genetic DNA sequencing will fall in the coming months and years with the development of next-generation (non-Sanger based) sequencing techniques. Therefore, we have explored the impact on the results of reducing the cost of sequencing by an estimated 40% (Dr Gail Norbury, Guy's Hospital, London, 2011, personal communication). In this scenario, LIPOchip (platform processed in Spain) becomes extendedly dominated. Elucigene FH20 is dominant and CGA is associated with an ICER of £995 per QALY gained relative to LDL-C.

Sensitivity relating to diagnostic test accuracy

For each of the main tests we have investigated the cost-effectiveness based on studies reporting the highest and lowest sensitivity values for Elucigene FH20 and for LIPOchip. This gives a greater picture of the uncertainty across studies and the impact on associated cost-effectiveness results. It also reflects the sensitivity of our analyses to different population groups, some of whom may have greater sensitivity on Elucigene FH20, with others doing better with LIPOchip.

In relation to Elucigene FH20, the upper limit of the sensitivity analysis (0.52[38]) increases the ICER associated with Elucigene FH20 relative to LDL-C. This suggests higher proportionate increases in costs relative to proportionate increases in QALYs, thereby increasing the ICER between the two tests. Lower estimates (0.286[36]) work in the opposite direction and lead to Elucigene FH20 being dominant over LDL-C. Such findings are somewhat counterintuitive, with there usually being a positive relationship between higher test sensitivity and improvements in cost-effectiveness. The situation here, however, is more complex because of the clinical benefit (and QALY gain) of LDL-C at minimal cost as well as the addition of cascade testing. Higher sensitivity tests lead to a greater number of positive relatives being given a targeted sequencing test (which is more expensive). Although this test detects more true FH cases and generates greater QALY gain, this is offset somewhat by the advantages of LDL-C (individuals will gain

improvements in QALYs regardless of whether or not they have FH, through statin-based therapy for their high cholesterol) that form part of the comparator testing. A similar situation arises with LIPOchip strategies relative to LDL-C. However, in all of these analyses, the rank ordering of Elucigene FH20, LIPOchip and CGA in terms of effectiveness and cost-effectiveness remains the same. As the sensitivity of Elucigene FH20 and LIPOchip increases, their associated ICERs approach that of CGA.

The sensitivity and specificity of LDL-C among relatives are taken from Starr and colleagues[49] and varied according to the upper and lower bounds of the 95% CIs. In both scenarios, Elucigene is the most cost-effective option relative to LDL-C. ICERs tend to be slightly lower for genetic tests using the higher bound of the CI for sensitivity and slightly higher for the lower bound. These differences are, however, small in magnitude and the counterintuitive effect of test sensitivity in relation to the ICER can be explained as discussed above. Similar analysis of the specificity of LDL-C among relatives does not alter the sequences of the ICERs or the conclusions drawn from the relevant comparisons. Again, all non-dominated sequences are highly cost-effective relative to LDL-C.

In conclusion, based on the above analyses, the results show some sensitivity to changes in some parameters and structure for the confirmation of index cases alone, but are more robust to variations in key parameters when index cases and relatives are analysed together. In all scenarios presented, Elucigene FH20, LIPOchip (Spain) and CGA are cost-effective uses of NHS resources relative to LDL-C. There is some uncertainty surrounding the direction of movement of the ICER as a result of changes in the sensitivity of the tests that may seem counterintuitive. The results of the one-way sensitivity analyses should therefore be interpreted with caution and, for a more accurate measure of overall model uncertainty, probabilistic sensitivity analysis is likely to offer a better estimate.

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis is carried out for the base case as described in the methods section. *Figure 12* illustrates the results in the form of a CEAC.

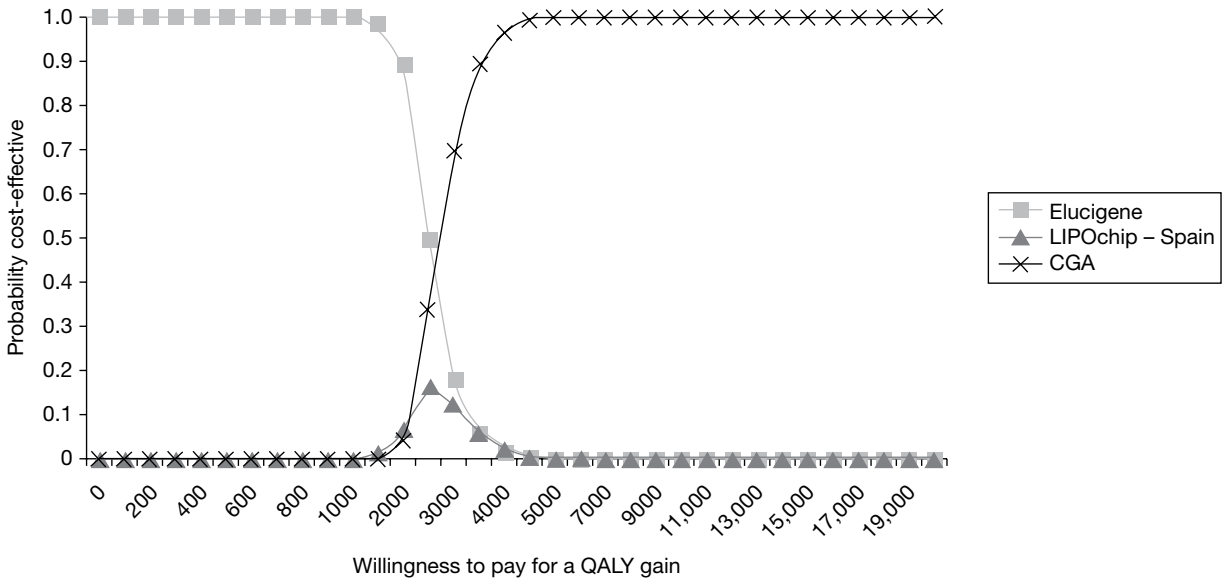

FIGURE 12 Cost-effectiveness acceptability curves for the base-case analysis.

This figure shows that, at low threshold values of willingness to pay for a QALY gain relative to LDL-C (< £2500), Elucigene FH20 has the highest probability of being cost-effective, but this reduces as the willingness to pay for an additional QALY increases. CGA is the most cost-effective option at threshold values > £2500 and is associated with a > 90% probability of being cost-effective at all threshold values > £3500 per QALY gained (*Figure 12* is scaled down to aid discussion of low threshold values). The other non-dominated strategy, LIPOchip platform processed in Spain, is never associated with a probability of cost-effectiveness > 20%. Probabilistic analysis also generates similar results and conclusions for each age subgroup in the analysis (see *Appendix 15*). At threshold values of willingness to pay for a QALY gain approaching £20,000, CGA is always the most cost-effective option. This is an important point and confirms the generalisability of the base-case probabilistic results to other age groups.

In addition to deterministic analysis surrounding the mutation detection rate among clinically diagnosed FH patients, we considered some extra analysis based on input from Dr Anthony Wierzbicki (Guy's and St Thomas' Hospitals NHS Trust, 2011, personal communication), who states that, among his patient group, the majority of patients are possible FH and he estimates that the proportion likely to be detected by CGA is approximately 20–25% or may even fall to 5% in some population groups. With this in mind, we have conducted probabilistic sensitivity analysis for a range of potential mutation detection rates for CGA. The relevant CEACs are presented in *Appendix 17* and show that the results are somewhat sensitive to this value in the model, especially at low threshold values and for lower rates of prevalence. For the lowest prevalence rate considered (5%), there is quite a bit of uncertainty at threshold values < £6000 per QALY gained. At very low values of willingness to pay (< £3000 per QALY), Elucigene FH20 is the strategy most likely to be cost-effective. LIPOchip platform processed in Spain is less likely to be cost effective except at very specific values of willingness to pay between £3000 and £4000 per QALY gained and at a low prevalence rate of 5%. However, this test is never associated with a probability of cost-effectiveness of > 50% regardless of prevalence rate or willingness-to-pay threshold. For higher estimates of prevalence (i.e. 10–50%), the results mirror those of the base-case analysis. However, of greater importance is that, for all prevalence rates of FH considered, CGA is the most cost-effective strategy at threshold values of > £5000 per QALY gained, increasing to 70% at the conventional value of willingness to pay of £20,000 per QALY gained for a prevalence of 5%. This probability increases to almost 100% for all other prevalence rates considered (i.e. 10%, 20% and 50%). Therefore, although there is some uncertainty surrounding the results based on varying mutation detection rates in clinically diagnosed index cases, probabilistic analysis shows CGA to be the most likely cost-effective use of NHS resources. The conclusion of the cost-effectiveness of CGA confirms the results of the previous NICE guidance in that the most comprehensive test for FH is cost-effective. NICE CG71[1] estimated that CGA was cost-effective with an associated ICER of £2676 per QALY gained versus LDL-C. Our results generate similar conclusions with a lower estimate of the ICER of £1030 per QALY gained relative to LDL-C. This is likely to be because of the cost reductions in CGA and in treatment over time.

Summary

Base-case results from deterministic analyses show that Elucigene FH20 is the most cost-effective diagnostic test, being less costly and more effective and thus dominant over LDL-C. However, this test strategy is less effective than recommended alternatives such as CGA (the most comprehensive diagnostic test for FH). Other non-dominated test strategies, LIPOchip platform processed in Spain and CGA, are also highly cost-effective. The latter strategy generates the greatest QALY gain but at additional cost. The sequences of the ICERs remain robust to the majority of deterministic sensitivity analyses; however, some plausible variations change the

magnitude of these ICERs slightly. It is likely that CGA will become more cost-effective going forward because of the emergence of next-generation sequencing techniques, reducing the time and cost required to conduct large gene sequencing operations. More important, though, is the fact that all three non-dominated test strategies are cost-effective at all conceivable threshold values of willingness to pay for a QALY gain. In all cases it is more cost-effective to cascade test relatives using targeted sequencing instead of either Elucigene FH20 or LIPOchip. This is because of the relative diagnostic cost savings for the same high level of accuracy in a targeted group of relatives.

Probabilistic sensitivity analysis more clearly shows the relative cost-effectiveness of the three test strategies mentioned above. At usual threshold values of willingness to pay for a QALY gain of £20,000, CGA is the most cost-effective test strategy. Although the probabilistic sensitivity analysis shows some uncertainties surrounding alternative mutation detection rates among clinically diagnosed index cases, CGA still remains the most likely option to be cost-effective. The probabilistic results are not sensitive to the age of the index case or associated average age of relatives.

Amongst the test strategies identified as being cost-effective, there are other factors that may need further consideration before arriving at a judgement on which strategy to recommend. For example, there may be practical and resource issues associated with full-scale implementation of CGA if this is recommended as a test strategy for all. If so, then judgement is required on whether it is ethical to implement cascading based on an index test result that is not as accurate as alternative more effective and cost-effective strategies such as CGA. In addition, cost-effectiveness will also depend on how clinicians view the outcome of tests such as Elucigene FH20, which detect only approximately 44% of cases with a FH-causing mutation; for example, there is the potential for missing cases, especially at-risk relatives who may not show high LDL-C levels when tested but who may have a FH-causing mutation. These patients may forgo potentially life-saving treatment if index cases are managed only on the basis of their clinical diagnosis as opposed to their genetic test. This issue does not arise for CGA for which an unequivocal diagnosis is reported in so far as this method detects all known FH-causing mutations.

Chapter 4

Assessment of factors relevant to the NHS and other parties

Factors relevant to the NHS

Funding of the DNA testing

The current NICE clinical guideline (CG71)[1] identifies DNA testing as the recommended method for confirming a clinical diagnosis of FH among Simon Broome definite FH and possible FH probands and also (and perhaps most importantly) the identification of first-, second- and possibly third-degree relatives of the index case for testing using a targeted sequencing test. However, findings from the 2010 audit of FH services[18] suggest that the current NICE guideline is not being widely implemented, primarily because of shortages in funding at a local level. The 2010 audit found that, although 97% of sites have access to an accredited laboratory for lipid measurement, only15% had access to funded DNA testing.

Our results confirm that CGA is the most sensitive testing strategy for identifying at-risk relatives and, based on the results from probabilistic sensitivity analysis, is likely to be the most cost-effective testing strategy. This is in line with recommendations from CG71.[1] CGA is, however, the most costly diagnostic test (although the cost implications can be partially offset against cost savings emanating from reduced cardiovascular events treated and more appropriate targeted treatments for these people). With concerns about access to funding for DNA testing being raised in the FH audit[18] there may be perceived barriers to the widespread adoption of CGA as the strategy of choice.

The adoption of less costly approaches than CGA is possible. Other non-dominated strategies also appear cost-effective at points below conventional willingness to pay for a QALY values. However, strategies such as Elucigene FH20 and LIPOchip are imperfect methods for detecting gene deletions and duplications, such that a MLPA test would be required with Elucigene FH20 and may well be pragmatically required in addition to LIPOchip to confirm the diagnosis for these cases. On the plus side, however, such strategies may be simpler and cheaper than CGA.

It is probable, however, that the cost of implementing testing with CGA will reduce in future years. It is estimated from previous guidance that the cost of cascade testing of all at-risk individuals would be approximately £12.913M per year[80] over 5–10 years, after which time costs would fall further as more and more of the current 100,000 or so patients with FH would be detected. After this 5- to 10-year period, cascade testing would be on a case-by-case basis of those who had not previously been tested. With reductions in costs associated with next-generation gene sequencing, these cost estimates have fallen over recent years and are likely to fall further in coming years. Additionally, atorvastatin therapy is coming off patent in 2011, which will also ease the financial burden of implementing the guidance. It may therefore be a more efficient use of NHS resources to adopt a comprehensive testing programme now to avoid the additional costs of delaying and retesting patients currently cascaded using LDL-C with genetic tests in the future. There may therefore be some savings to the NHS that have not as yet been identified. It is difficult to quantify such potential savings as this would depend on future NICE guidance and whether or

not primary care trusts implement the current guidelines as per CG71[1] to use at least some form of DNA testing strategy.

Financial burden to NHS of (as yet) undiagnosed patients

The NHS needs to be aware of the financial burden of the significant number of individuals (estimated to be around 100,000) who have FH and are as yet undiagnosed (but who would subsequently be diagnosed through cascade testing). The management and treatment of these cases, once identified, will generate a significant resource burden to already tight NHS budgets. Also, it is unclear whether or not the capacity currently exists in lipid clinics to identify cases, trace family history and refer all those requiring testing. Clinical expert opinion suggests that capacity is available within the genetics laboratories in the UK to conduct all relevant tests.

Factors relevant to other parties

Benefits to individuals of a definitive diagnosis

Should the widespread implementation of cascade testing be achieved in the UK, there are a number of benefits that individuals identified with FH through that process can expect to incur. For example, appropriate treatment can be started quickly, cholesterol levels can be monitored and managed, the risk of getting CHD and having a heart attack is reduced and close family members can be screened and treatment started if necessary. It is also known that, if treatment can be started early, before CHD is established, this reduces the risk of dying prematurely.[2]

Possible adverse sequelae of a definitive diagnosis

Despite the benefits that a definitive diagnosis can bring, it is also well known that psychological sequelae can arise for individuals and their family following the formal diagnosis of a clinical condition. There are issues of anxiety associated with being diagnosed with a genetic disease; however, equally there may be a sense of closure for the patient, who will be able to proceed with an action plan to manage his or her FH using appropriate treatment methods. Although no evidence exists linking psychological impact to QALY gain for FH patients, as FH is very treatable once identified, it is likely that the psychological impact of the genetic testing would be positive for the patient. Individuals, especially parents, may also gain positive views from the knowledge that a relative, especially their children, will be treated correctly should they be diagnosed with FH.

Insurance for those diagnosed with familial hypercholesterolaemia

If you are being treated for a medical condition you usually have to declare it to your insurance company, otherwise it could invalidate your insurance. Having a diagnosis of FH may affect how a person is treated when they apply for life assurance or travel insurance and could also have an impact on mortgage applications. Some insurance companies may decide that a person with FH has a higher risk of getting CHD and may charge higher premiums. Also some insurance companies may not differentiate between high cholesterol as a result of poor diet and other lifestyle factors and high cholesterol caused by an inherited condition such as FH.[2]

Other issues

The use of strategies involving Elucigene FH20 and/or LIPOchip could provide advantages to patients in terms of early detection of disease and provision of an unequivocal diagnosis, allowing cascade testing for the early identification and treatment of relatives. Although the benefits of such tests in achieving a definitive diagnosis are clearly evident, there are some ethical and equity issues arising from the recommendation of a less than fully sensitive and specific genetic test. As reported in *Chapter 3* (compared with LDL-C), although strategies such as Elucigene FH20 or

LIPOchip (platform processed in Spain) appear to offer a cost-effective use of NHS resources at less than usual threshold values of willingness to pay, their recommendation as a single test may raise ethical concerns. Elucigene FH20 and LIPOchip both detect a limited set of FH-causing mutations. Owing to concerns over LIPOchip's ability to detect copy number changes as accurately as MLPA, some relatives of index cases with less commonly occurring mutations may go undetected. Such individuals would be disadvantaged owing to the documented inadequacies of the use of LDL-C to give a definitive diagnosis of FH.

Chapter 5

Discussion

The first section of this chapter includes discussion of diagnostic accuracy test performance (see *Chapter 2*); this is followed by discussion of the results of the cost-effectiveness analysis (see *Chapter 3*).

Discussion of test performance results

Statement of principal findings

Fifteen studies were included in this assessment. Three studies (four reports) evaluated Elucigene FH20, five studies (six reports) evaluated various versions of LIPOchip, four studies reported data on the performance of LDL-C as a part of the Simon Broome criteria or LDL-C cut-offs of > 4 mmol/l and three studies reported age-and gender-specific LDL-C cut-offs for cascade testing of relatives.

Elucigene FH20 and LIPOchip studies

The included studies on Elucigene FH20 and LIPOchip reported a sequential genotyping test in which (1) the participants received a clinical diagnosis of FH followed by the index test (as a pre-screen) and then (2) those who tested negative received further genetic investigations such as gene sequencing and MLPA. CGA was the reference standard considered in the review. Assessment of the methodological quality of the included studies showed that overall the participants were representative of those who would receive the tests in practice.

Based on the data from the included studies we were able to deduce true-positive, true-negative and false-negative rates for each test. False-positive results could not be derived for any of the studies evaluating Elucigene FH20 or LIPOchip as only those who initially tested negative went on to receive the reference standard. Therefore, only sensitivity, and not specificity, of Elucigene FH20 or LIPOchip could be deduced and reported (sensitivity represented the percentage of cases with mutations found by CGA that are also detected by the candidate test).

Because of the sparse data on overall clinical diagnosis and variability in the LIPOchip versions used, sensitivity data could not be pooled. Therefore, we have provided a narrative overview and graphical presentation of the diagnostic performance of Elucigene FH20 and LIPOchip.

Low-density lipoprotein cholesterol studies

In general, the included studies on LDL-C (as part of the Simon Broome criteria for the diagnosis of probands or age-and gender-specific LDL-C cut-offs for the diagnosis of relatives as recommended by NICE guideline CG71[1]) provided data on true- and false-positives and -negatives, allowing the calculation of both sensitivity and specificity. Again, because of the variability in both the clinical diagnosis and the comprehensiveness of the genetic tests used, sensitivities and specificities could not be pooled to provide a single estimate.

Diagnostic accuracy

The sensitivity of Elucigene FH20 and LIPOchip in detecting FH varied. Amongst UK populations with a clinical diagnosis based on the Simon Broome criteria, Elucigene FH20 was reported to detect 44% and 52% of those with FH-causing mutations that were detected

by CGA. The UK has a population with a wide mutational spectrum and, as Elucigene FH20 is designed to detect a limited number of mutations, the sensitivity of the kit is largely dependent upon the prevalence of these specific FH-causing mutations in the population, hence resulting in variations. For example, predicted sensitivities of 32% in Wales[48] and approximately 33% in Aberdeen, Scotland (prevalence with CGA 28%),[79] were reported for Elucigene FH20 (by tallying the mutations that are covered in the Elucigene kit against the mutations that were picked up by CGA in those setting), which is lower than sensitivities reported by included studies. Moreover, it has been suggested that interpretation of the Simon Broome diagnostic criteria is not uniform throughout the lipid clinics in the UK and this may also lead to variation in the detection of FH.[70]

Variation was observed across countries in the sensitivity of Elucigene FH20 in detecting FH in those with a clinical diagnosis of definite FH. Elucigene FH20 showed sensitivity of 49% in confirming FH in those with a clinical diagnosis of definite FH in a UK population (the prevalence of FH in the study was 28%), whereas sensitivity of only 29% was observed in an Australian population in which the prevalence of definite FH in the study was very high (78%). These differences could possibly be explained at least in part by the following two factors: (1) mutations included in the Elucigene FH20 kit were selected based on their frequencies in a sample of around 400 patients who were diagnosed as definite FH based on a Simon Broome diagnosis[26] and (2) differences in the definitions of definite FH used in the two study populations (in the Dutch criteria a clinical diagnosis of definite FH does not require the presence of xanthomata, unlike the Simon Broome criteria).

The sensitivity of LIPOchip ranged from 33.3% (UK population) to 94.5% (Spanish population) using various versions. Using LIPOchip version 8, which contains 251 of the mutations most prevalent in a European population, the sensitivity observed in a UK population with a clinical diagnosis of FH based on the Simon Broome criteria ranged from 33.3%[40] to 56.9%,[41] while specificity was reported as 93.8%.[40] It should be noted that LIPOchip version 8 does not detect five mutations that are detected by Elucigene FH20 and which are common in the UK population; therefore, the sensitivity of the UK version of LIPOchip is likely to be higher. In the version of LIPOchip including frequent UK mutations (version 10), sensitivity would be improved to 78.5%[41] (Progenika, personal communication) in detecting FH in a UK population. However, this was based on a very small sample size ($n = 120$) and only those with a confirmed genetic diagnosis were included and therefore the results should be interpreted with caution. None of the included LIPOchip studies reported accuracy data separated by definite FH or possible FH.

The sensitivity of LDL-C as part of the Simon Broome criteria compared with CGA was high (90–93%); however, specificity was low (28–29%) with a large number of false-positives observed. Nevertheless, only four of the LDL-C studies (three full text and one abstract) used the most complete CGA as defined in the assessment. The implications of this high false-positive rate are that potentially unnecessary additional tests or treatments may be given to those who do not have (genetically diagnosed) FH.

A risk of 10–20% of either incorrect diagnosis or misdiagnosis of FH has been reported.[81,82] In the UK, an overlap in LDL-C distributions amongst those with and without FH has been reported. It has been suggested that, because of the overlap in LDL-C levels, no cut-offs are 100% accurate.[22] Mabuchi and colleagues[46] reported higher accuracy of LDL-C using a cut-off of 4.1 mmol/l (sensitivity and specificity of > 98%) among genetically diagnosed FH patients and unaffected relatives in Japan. The mean LDL-C levels amongst those with and without FH may differ from country to country, with some studies reporting an overlap in LDL-C distributions while others do not.[49] In the study by Mabuchi and colleagues[46] the mean LDL-C level was 6.7 (SD 1.52) mmol/l in those with FH compared with 2.97 (SD 0.65) mmol/l in those without FH, with

almost no overlap in LDL-C distributions. This could partly explain why using a LDL-C cut-off of 4.1 mmol/l was found to be highly sensitive in this population.

Cascade testing

In a family with FH, 50% of first-degree relatives are likely to have the condition. One of the advantages of genetic testing is that, if a mutation is identified in probands, targeted gene sequencing can be used in cascade testing of relatives to detect the culprit mutation and provide an unequivocal diagnosis of FH. Using targeted gene sequencing, the observed detection rate of FH in relatives ranged from 53% to 56% in two studies,[37,45] which is broadly consistent with rates reported by others (37–56%; see *Appendix 18*).[11,19,67,83–85] A study by Wiegman and colleagues[50] reported that a high detection rate (77%) in children from families in whom a mutation was identified in probands was observed through targeted sequencing. However, the authors of the study suggested that one possible reason for the high detection rate was that siblings with very low LDL-C levels were not taken to the clinic to undergo targeted sequencing. Moreover, children are present with monogenic causes of hypercholesterolaemia and are likely to have a higher detection rate of FH-causing mutations.

High sensitivity and specificity of age- and gender-specific LDL-C cut-offs compared with CGA were reported in cascade testing of relatives, suggesting the clinical utility of this approach in the absence of genetic diagnosis. In the study by Lee and colleagues,[48] 91% sensitivity and 93% specificity of cascade testing of relatives were reported using age- and gender-specific LDL-C cut-offs, although one explanation for the high values reported is that the included index participants were all homozygous for FH. In a subgroup analysis, Wiegman and colleagues[50] reported sensitivity of 96% using LDL-C cut-offs of ≥ 3.5 mmol/l in children of parents with a clinical diagnosis of definite FH.[48,50] The authors of the study suggested that this sensitivity would apply to those children in a family with definite diagnosis of FH only.

Strengths and limitations of the assessment

In terms of strengths of the assessment, screening of articles and quality assessment of full-text papers were performed independently by two reviewers. Conference abstracts were included. To avoid missing potentially relevant studies reporting Elucigene FH20 or LIPOchip, in addition to studies reporting a clinical diagnosis of FH based on the Simon Broome criteria, those reporting a clinical diagnosis of FH based on the Dutch or MedPed criteria were also included. We also contacted study authors to obtain clarification on aspects of their reports or in an attempt to obtain missing data.

In terms of limitations of the assessment, non-English-language studies were excluded. A limitation of the literature was that, because the tests evaluated are still new and evolving, a limited amount of evidence was identified reporting Elucigene FH20 and LIPOchip in a UK population, with sample sizes as low as 22 patients[40] and not all published as peer-reviewed full reports. One possible mechanism we could have adopted to indirectly infer additional information on the tests would have been to back-calculate data from those studies that had undertaken CGA (by tallying the mutations that are covered in the Elucigene FH20 kit or LIPOchip kit against the mutations that were picked up by CGA) and thence calculate the predicted sensitivity of the tests. However, because of time constrains we were unable to do so. Also, we would have had to acknowledge the inferred nature of those calculations had they been undertaken.

The available evidence varied in terms of the diagnostic criteria used to provide a clinical diagnosis of probands, the versions of LIPOchip used, the comprehensiveness of the genetic analysis (specifically for studies reporting LDL-C compared with CGA) and the threshold of

LDL-C cut-offs used to define a positive test result. Because of this heterogeneity it was not considered appropriate to calculate pooled estimates.

Methodological quality of the included studies

We did not find any studies that directly compared Elucigene FH20 and/or LIPOchip with LDL-C (either as part of the Simon Broome criteria for the diagnosis of probands or age- and gender-specific LDL-C for the diagnosis of relatives) against a reference standard of CGA. A RCT[86] (and its secondary report[84]) was identified, conducted in the UK, in which all participants received a clinical diagnosis based on the Simon Broome criteria and one group received a genetic test while the other received a LDL-C test using Simon Broome cut-offs. However, there were insufficient data to calculate the sensitivity and specificity of these tests in index cases, and also Simon Broome LDL-C cut-offs were used in testing relatives instead of age- and gender-specific LDL-C cut-offs; hence, this study was excluded from the assessment.

All of the included studies were cross-sectional in nature, with only two studies recruiting consecutive patients.[37,44] Abstracts were not quality assessed as they were not considered to contain sufficient information to allow for an adequate assessment of study methodology. In all but one study (LDL-C test[46]), patients were representative of the spectrum of those who would receive the test in practice. These were patients with a clinical diagnosis of FH based on the Simon Broome, Dutch or MedPed criteria or, for cascade testing, the relatives of those index cases with a confirmed clinical diagnosis of FH. The results from studies in which participants are clinically diagnosed based on the Simon Broome criteria would be of specific interest to UK practice.

An incomplete genetic testing strategy may result in mutations not being detected because of the limitations of the testing strategy. Only one study reporting Elucigene FH20,[37] one study reporting LIPOchip[39] and 50% (three out of six) of the LDL-C studies[44,45,49] used genetic analysis that comprised DNA sequence analysis of the *LDLR* and *APOB* genes in conjunction with MLPA. Given that the FH-causing *PCSK9* gene is rare and was discovered only fairly recently, those studies that otherwise met the definition of CGA but without assessing the *PCSK9* gene were judged to include an acceptable reference standard in terms of classifying the target condition in this assessment. However, only two of the above studies that employed CGA did not perform *PCSK9* analysis.[45,49] With respect to the reference standard used, all six abstracts (two reporting Elucigene FH20, three reporting LIPOchip and one reporting LDL-C) used adequately defined CGA, which comprised DNA sequence analysis of the *LDLR* and *APOB* genes (plus *PCSK9* gene) in conjunction with MLPA that was likely to classify the target condition.

In the Elucigene FH20 and LIPOchip studies, only those who tested negative went on to receive further genetic investigations; thus, none of the test-positives received the reference standard (differential verification bias), giving rise to the possibility of overestimation of test performance. Because of the sequential nature of the tests used, these studies were also at risk of partial verification bias as neither the whole sample nor a random sample received verification with a reference standard. All of the LDL-C studies were free of partial verification bias and one was free of differential verification bias.[44] Test review bias (the results of the index test are interpreted with knowledge of the results of the reference standard test) was avoided in the Elucigene FH20 study, one of the LIPOchip studies and two of the LDL-C studies. It has been suggested that both test review bias and diagnostic review bias (in which the results of the reference standard test are interpreted with knowledge of the index test) may lead to higher values being reported for sensitivity.[87] However, these biases are of more importance in tests in which the results are based on subjective interpretation rather than automatically generated.

Uncertainties

The spectrum of patients considered in this assessment was those with a clinical diagnosis of either definite or possible FH (including relatives of confirmed FH cases). Therefore, any evidence from this review is not generalisable to the wider, asymptomatic general population. The inclusion of population-based screening studies was beyond the scope of this review.

Assessment of a new technique – iPLEX – was also beyond the scope of this review as this was not CE marked at the time that the review was conducted. iPLEX is a rapid genetic testing kit developed to cover 56 mutations (54 in the *LDLR* gene, one in the *APOB* gene and one in the *PCSK9* gene) most commonly found in the UK population. It has been reported that this kit has an average detection rate of 75% ($n = 150$ patients) with a false-positive rate in a 'no mutational control group' of 0.015%,[88] and that the kit can produce a test result within 1 hour.

Analysis of the sensitivity of Elucigene FH20 and LIPOchip in relation to homozygous or compound heterozygous FH was similarly beyond the scope of this assessment. People with compound heterozygous FH carry more than one mutation and pre-screening with Elucigene FH20 or LIPOchip may miss the second mutation if it is not covered by the genetic testing kit and genetic testing stops after the first mutation is identified. In such circumstances relatives of the diagnosed proband may carry a different mutation to the one identified by the pre-screen and could be misdiagnosed as non-FH if only the mutation identified on the pre-screen is checked in cascade testing of relatives. A case study by Taylor and colleagues[89] reported that compound heterozygous FH gave rise to a severe phenotype and suggested that the presence of additional mutations in families should be considered when relatives have varying phenotypes. Although such FH cases are very rare in the UK, with a prevalence of around 1 in 1 million, recognition of the issue is important.

A wide range of approximately 30[27]–95%[90] of patients with a clinical diagnosis has been reported to have a mutation confirmed by genetic diagnosis. In some people with FH the results of CGA might still be negative because full sequencing of the *APOB* and *PCSK9* genes is not routinely undertaken, and there may be other genes as yet unrecognised that give rise to the FH phenotype. Moreover, a number of other high-penetrance genes may harbour quite rare mutations (as is emerging in schizophrenia) or alternatively familial clustering of low-penetrance alleles may cause a FH phenotype, as reported in familial breast cancer. The recent report found that approximately 95% of children meeting the Dutch criteria for FH had a genetic mutation,[90] whereas only approximately 30[27]–50%[37] of patients meeting the Simon Broome criteria had a mutation confirmed by genetic diagnosis.

None of the included studies reporting Elucigene FH20 or the LIPOchip UK version provided information on clinical effectiveness outcomes. Other studies have shown clinical improvements in patients in whom the diagnosis of FH has been confirmed after cascade screening.[11,19] In a large genetic screening study with 1 year of follow-up, a very high proportion of patients (93%) identified with FH started on lipid-lowering medication, showing the effectiveness of the genetic testing.[19] Significant reductions in TC and LDL-C were observed in those with identified FH 6 months after genetic screening.[11]

Other relevant factors

Psychological impact and acceptability of genetic testing

Evidence has suggested that genetic diagnosis of FH has no clinically relevant adverse psychological effects.[11,91] A RCT conducted in the UK that included probands with FH and their relatives found that there was no significant effect of genetic diagnosis on perceptions of control over FH, fatalism of FH, control over cholesterol or control over heart disease and adherence to

risk-reducing behaviour; however, those with a confirmed genetic diagnosis had a strong belief in the efficacy of cholesterol-lowering drugs and a less strong belief in the efficacy of diet.[86] Another prospective comparative study conducted in the Netherlands among participants in a family-based genetic screening programme, however, found that those with an identified mutation perceived that they were at greater risk of heart disease than those with no mutation. The result was influenced by age, education, cholesterol level and cardiovascular disease in the family.[92]

Cascade screening studies have reported high participation rates of 73[11]–90%.[19] In a UK cascade screening study in Oxfordshire, 97% of parents asked for their children to be screened.[93] In terms of approaches used, directly contacting relatives from clinics has reported higher participation rates[19] than contacting relatives through probands.[93] Using both approaches resulted in a higher participation rate (73%) than contact through probands but was not higher than directly contacting relatives. However, there may also be concerns about the possible consequences of receiving a positive genetic test result. In a large genetic screening study in the Netherlands, 10% of individuals declined genetic testing because of the fear of negative effects on employment or insurance.[19]

Although genetic diagnosis may be generally acceptable to patients, for clinicians making a diagnosis of FH still remains a challenge and dependent upon their judgement in circumstances in which patients have raised cholesterol levels but no identified FH-causing mutation.[94]

Risk associated with different types of mutation

Based on the lipoprotein levels, mutations have been categorised as either 'severe' (functional null alleles and missense in exon 3/4; or functional null alleles plus splice variants) or 'mild' (missense outside exons 3/4 and splice; or any missense mutation).[84] A null mutation has been identified as one of the important risk factors associated with PCVD in FH patients.[43,95] A significantly higher risk of PCVD, recurrence of cardiovascular events and family history of PCVD was reported in patients carrying null mutations compared with patients with defective mutations.[95] The relative risk of PCVD in patients with a null mutation was 3.1 times higher than that in patients with a missense mutation.[43] The mean PCVD-free survival time in those with null mutations was 51–53 years, in those with missense mutations was 58 years and in those carrying defective mutations was 53 years ($p < 0.01$).[43,95]

Taylor and colleagues[37] reported a similar prevalence of severe mutations across study participants with a clinical diagnosis of definite FH, possible FH and also unclassified FH.

Discussion of cost-effectiveness results

Statement of principal findings

Index cases only

The base-case analysis refers to an index case aged 50 years and a mutation detection rate for FH equal to 36.5% of cases with a Simon Broome possible or definite FH diagnosis. With regards to the identification of index cases alone, Elucigene FH20 was the least costly test but also generated the least QALY gain because of the high number of false-negatives associated with this test. Accounting for the inclusion of both diagnostic and treatment costs (including clinical management), LDL-C was the most costly option for index cases alone but also generated the greatest number of QALYs gained. The reason for this is that all patients who meet the Simon Broome clinical diagnosis of FH will have elevated cholesterol levels as part of that diagnosis. The diagnosis is not definitive but patients with false-positive test results on LDL-C for FH will still gain from statin therapy on the basis of them having high cholesterol; the difficulty, however, with this strategy arises when cascade testing incorrectly takes place from false-positive index cases.

Index cases and relatives

Of greater relevance, however, to the decision problem is the identification of at-risk relatives of index cases in whom cascade testing should be carried out. Each 50-year-old index case will have on average five first-degree relatives, four second-degree relatives and four third-degree relatives still alive and eligible for contact for cascade testing. These numbers refer to the base-case scenario and will vary depending on the average age of the index case. For example, older people may have more second-degree relatives eligible for testing as they are likely to have living grandchildren. Similarly, younger people will have more grandparents alive than an index case aged 50 years. This variation is incorporated in the model results.

In the analysis of index cases and relatives, LDL-C as a stand-alone test is the least costly testing option. CGA dominates pre-screen tests also including CGA as part of the strategy of testing. This is because of the assumption that QALY gains for FH are not time sensitive and the extra time taken to deliver a tiered-strategy diagnostic test will have no implications for treatment or QALY impact. This suggests that, although pre-screen tests such as Elucigene FH20 and LIPOchip (Spain) are less costly in their own right, they do not offer overall cost savings as a pretest to CGA, suggesting that the extra costs associated with running negative samples through all tests in a sequence outweigh the cost savings of those detected as positive on either Elucigene FH20 or LIPOchip. Only at very specific prevalence and sensitivity combinations would Elucigene FH20 be a cost-effective pre-screen to CGA. As the cost of gene sequencing falls in the future, it is less likely that targeted tests (at current prices) will offer a cost-effective pre-screen strategy for the majority of the population in whom testing would be carried out.

Of greater interest, however, is the comparison of the non-dominated tests with the relevant comparators for this assessment. CG71[1] recommended that DNA testing in combination with LDL-C testing was the most cost-effective strategy to test index cases and identify relatives for cascade testing. However, in practice, uptake of DNA testing for FH has been very slow, especially in England, where the 2010 FH audit[18] suggests that only 12% of trusts have access to a formal system of cascade testing, with a further 14% stating that such a system is in development. One issue for this may be a lack of funding in the area, and clinical advice suggests that, in reality, LDL-C testing in combination with the Simon Broome criteria is a more realistic reference standard for this assessment. With this in mind, the main comparison of non-dominated sequences is with LDL-C. However, we also report sequential results ordered by cost and a comparison of cost and QALY differences against CGA for completeness.

When compared with LDL-C, CGA is a highly cost-effective diagnostic test and is the only option that gives an unequivocal diagnosis of FH. This strategy is estimated to cost £1030 per QALY gained relative to LDL-C and thus at usual thresholds would appear to be a highly cost-effective use of NHS resources, and this is further confirmed through probabilistic sensitivity analysis. This finding is in agreement with similar findings from NICE clinical guideline CG71,[1] which also found that DNA testing was highly cost-effective in the identification of relatives of index cases with FH. As reported in *Chapter 2*, there is always the potential that there exist undiscovered genetic mutations and culprit genes that may lead to FH. For this reason, cascade testing would be carried out from mutation-negative index cases using LDL-C testing as they are still technically FH positive based on their clinical diagnosis.

The LIPOchip manufacturer, Progenika, offers a service for testing samples in Spain. This platform offers LIPOchip as a pre-screen and a follow-up screen of all negative samples using sequencing of the *LDLR* gene. As LIPOchip tests for duplications of and deletions in the gene, this may be described by the manufacturer as CGA; however, there is much clinical uncertainty in relation to the accuracy of the LIPOchip method of detecting deletions and large rearrangements of the gene. Additional evidence suggests that LIPOchip will correctly detect only

two out of seven exon copy number changes compared with MLPA.[69] The authors acknowledge that these data are based on small sample numbers; however, they raise further questions with regard to the accuracy of LIPOchip compared with MLPA. Therefore, MLPA would also be required to obtain a completely unequivocal diagnosis. The LIPOchip platform, processed in Spain, does not offer MLPA as part of the process and so it is assumed that the diagnosis obtained from this strategy would be inferior to that of CGA as described in this analysis. As this platform is slightly less sensitive, it is likely that there will be more uncertainty in the test result in about 5% of patients in whom the MLPA test would be required for additional confirmation. The LIPOchip platform processed in Spain is also found to be a cost-effective strategy, with an ICER of £871. Information provided by the manufacturer of LIPOchip suggests that 80.5% of index cases would be detected using the LIPOchip test and the remaining 19.5% would need gene sequencing to confirm the diagnosis (Progenika, 2011, personal communication to NICE). These figures refer to a definite FH sample being tested. However, it is estimated that of all the samples presenting for genetic testing, only 30–50% will have an identifiable mutation. Therefore, the estimates of cost provided by the manufacturer may have underestimated the number of samples testing negative on the LIPOchip test that would also require gene sequencing as the second stage of analysis. Equally, it may be that these costs would be reasonable because of manufacturer economies of scale. Should this strategy be recommended, it is imperative that the issue of price be confirmed before any decision is made.

The results do, however, suggest that if the recommendation to undertake CGA for all was considered impractical or too expensive (e.g. sufficiently large increases in CGA testing might lead to a requirement for extra laboratory space and associated infrastructure, not captured by the existing unit cost assumptions) and an alternative test (Elucigene FH20 or LIPOchip platform) is deemed appropriate, then either or both could be recommended. The test chosen for a particular population would pragmatically reflect the sensitivity of each of these tests within a particular clinic catchment area as it is found that tests may perform differently on groups of different ethnic origin. It may also reflect local resource conditions and clinical judgement, as there is a trade-off between costs and effects. The difficulty, however, in adopting such a strategy is that not all tests detect all individuals. Therefore, should any of these less-than-perfect testing strategies be accepted, they may miss out a number of potentially important cases. This may raise ethical and equity concerns as only a proportion of people will have the culprit gene identified and have their relatives followed up for genetic cascade testing.

The economic model results are more sensitive to changes in parameters for index cases alone than for index and relative cases together. As the latter is the main focus of the analysis of this project, these results are given the most weight in the discussion and reporting of results.

Relative to the comparator of LDL-C, probabilistic sensitivity analysis reveals that CGA is the most cost-effective diagnostic test strategy for the identification and testing of relatives with FH, with a probability of cost-effectiveness of > 90% for all age groups at all conventional values of willingness to pay for a QALY gain. Some variation is identified in the probabilistic analysis based on mutation prevalence rates, which may vary greatly in practice between different geographical areas. Although there is some variability in the results at low threshold values and at very low mutation prevalence rates, CGA does, however, remain the most likely strategy to be cost-effective relative to LDL-C (never dropping to < 50% probability at threshold values of societal willingness to pay of > £5000 per QALY gained).

Strengths and limitations

The economic analysis has a number of strengths and limitations for the confirmation of FH among index cases and the identification of first-, second- and possibly third-degree biological relatives for cascade testing. As the modelling processes used to generate this economic model

are adapted from a previously developed Markov model for these patient groups, many of the relevant strengths and limitations of this economic evaluation have already been reported in appendix E to the NICE clinical guideline CG71.[1] In addition to those already reported and published, the following discussion relates explicitly to additional issues relative to the model that may not have been reported elsewhere.

Strengths

This work is important and builds on the health economics evidence generated as part of the NICE CG71 development process.[1] This economic modelling exercise identifies a range of potential diagnostic strategies that were not available for the CG71[1] assessment (namely LIPOchip and Elucigene FH20) and investigates their cost-effectiveness either as stand-alone tests or as pre-screens to reduce costs associated with CGA. However, one issue of importance is that the cost of CGA, and gene sequencing in particular, has fallen since the CG71[1] assessment and is likely to fall still further with the evolution of next-generation sequencing. This favours the CGA approach and means that, in the future, going forward, the costs of gene sequencing may well fall further with the evolution of new methods and new technologies. However, even at current prices (approximately £480 per test), CGA is still a cost-effective method of cascade testing. It is the most cost-effective strategy in terms of attaining an unequivocal genetic diagnosis of FH among index cases and for cascade testing those relatives at greatest risk of having the disease. The analysis considered all currently available and approved diagnostic tests and linked test accuracy with final treatment outcomes measured in terms of QALYs. As additional tests become available, it will be possible to incorporate these into the model and re-run the analysis incorporating newly available evidence and tests.

The model structure is a key strength of the analysis in that it presents a linked evidence approach linking intermediate outcomes (i.e. diagnostic accuracy of each testing strategy) to the associated lifelong costs and health outcomes associated with each test result and whether tests were true-positive, false-positive, true-negative or false-negative. This was explored for a total of 12 alternative testing strategies through decision tree and Markov model analysis.

A structured literature search was carried out to identify existing cost-effectiveness evaluations of these tests and of the cascade testing of relatives. No studies directly compared the interventions under consideration, and only one study detailed the cost-effectiveness of any of the new interventions relative with no testing. This referred to the LIPOchip test but was used in relatives. As targeted sequencing is a much lower cost method of testing identified relatives, this LIPOchip study was not relevant to this analysis. Our results, however, do confirm the findings from a number of other studies evaluating the cost-effectiveness of the cascade testing process more generally and also the findings of the previous NICE guideline.[1]

Methods used to identify and obtain parameter estimates for the economic modelling sought to identify and utilise published sources and best available information; however, this was not possible in all cases. In such scenarios, for example the proportion of patients receiving various statin therapies and how treatment changes based on diagnosis, we have relied on clinical expert opinion from two or more clinical experts. Estimates of parameters are also sourced from the CG71[1] analysis where available and tested in sensitivity analyses.

Limitations

The model structure focused on the identification and treatment of index cases and relatives of index cases with FH as clinically diagnosed using the Simon Broome criteria. The costs and benefits of identifying other causes of similar symptoms have not been modelled in detail with the exception of the prescription of statin therapy for all index cases with high cholesterol levels. The impact of additional therapies such as diet, exercise, smoking cessation, etc. has not been

included and is beyond the scope of this assessment. The effect of not including such detail in the model is uncertain; however, it is generally widely acknowledged that all patients with a clinical diagnosis of FH will require some form of active treatment, generally statin therapy.

Another challenge related to the analysis of subgroups of the population, especially in relation to FH in children. Relative risks associated with children aged 15 years are assumed to be similar to those of adults aged 30 years. There is little evidence linking the efficacy of statins directly to cardiovascular events avoided, and for this reason we have assumed risks similar to those of a 30-year-old in the model. This probably creates some uncertainty in the estimation of quality of life in this subgroup of the population. Although data do exist relating to clinical outcomes in children (i.e. TC level), these are not linked directly to cases avoided. As Avis and colleagues[96] show, statins are efficacious in reducing cholesterol in children with FH and are not associated with significantly different adverse events to placebo; it is therefore assumed that health effects are similar to those of the next youngest age group in the model (aged 20–39 years). It is unlikely that this assumption greatly impacts on the cost-effectiveness results and associated conclusions drawn.

In terms of the estimation of costs for each testing strategy in the economic model, we have used the MOLU classification system to assign tests to bands and apply MOLUs to each band. This is an agreed costing mechanism devised by the UKGTN and CMGS with some built-in flexibility in pricing for each laboratory's individual circumstances. This is not necessarily an accurate reflection of true economic costs or indeed opportunity costs associated with testing for FH. However, in the absence of price data for all combinations of tests considered, robust costing methods for genetic testing for FH or a NHS tariff for the tests as well as uncertainty surrounding variability from laboratory to laboratory, it was impossible to cost all testing strategies fairly using any other universally acceptable approach. Using the cost of the test alone would be insufficient as it would not account for staff time and consumables required. Therefore, although acknowledging its limitations, we have on the basis of expert opinion relied on the MOLU system for the estimation of diagnostic testing costs in the economic model. Studies retrieved from the cost-effectiveness searches showed great variability in the costs of testing for FH. The reason for this is that testing for FH and genetic testing more generally is a rapidly evolving discipline. Many studies presented alternative definitions of DNA testing and the costs of completing the tests have fallen almost yearly in recent years. Therefore, older estimates would be an overestimate of the true costs. This is another reason why the MOLU system was used for this assessment.

A number of other assumptions were made in relation to the clinical management of patients with and without disease. Much uncertainty exists among clinicians in the treatment of FH, with many advocating a start low approach followed by an increase in treatment intensity if a satisfactory response is not achieved. Others believe that, as statin therapy generates very few adverse events, it would be appropriate to treat everyone with a high-intensity statin (e.g. atorvastatin). The impact of this uncertainty is explored in sensitivity analyses and is found not to alter our base-case results and conclusions, with only very small differences in ICERs.

Further, in relation to the utility of diagnostic information, there is no published evidence that links the outcome from the results of a genetic test for FH (e.g. increased anxiety) to quality-of-life outcomes and hence QALYs gained. A number of plausible scenarios are possible, including reduction in QALYs emanating from the shock of knowing that one has a genetic disorder. Equally, however, people diagnosed with FH could gain some reassurance from the fact that they know what is causing their illness and can aim to develop a plan of action in dealing with this. Additionally, parents may place a positive value on knowing the source of a child's illness. It is, however, likely that these factors would cancel each other out or favour genetic testing and would be much smaller in comparison with the QALY gains associated with being treated for a life-threatening condition such as FH.

An additional limitation of our analysis is that it is on an average patient level. We are aware that some mutations cause greater harm and are associated with greater risk of cardiovascular events. For example, mutations of the *PCSK9* gene are associated with greater clinical risk. Also, there are differences between missense and nonsense genetic mutations. Although these are likely to have implications for the prognosis of individual patients, this has not been modelled as there is insufficient evidence available to estimate how this would impact on quality of life. Further, as cost and QALY differentials are based primarily around treatment decisions and the general insensitivity of the model to small changes, it is unlikely that analysing the data on a mutation level for the purposes of cost-effectiveness would generate great differences in results or conclusions. Further, such data would be available for only few if any mutations and the inclusion of these only would generate further 'noise' into the analysis.

There are limited data available for the sensitivity of the LIPOchip test, with wide variation in all of the reported studies for various versions of the test. This generates a lot of uncertainty surrounding the true sensitivity of LIPOchip as used to populate the economic model. As many of the tests were analysed at the manufacturer's own laboratory, there is a lack of academic peer-reviewed information on this input for the economic model. To deal with the associated uncertainty we have conducted wide variation in the probabilistic sensitivity analysis, which should counter any biases that may have arisen as a result of a lack of critique of the estimate of sensitivity used for LIPOchip version 10 in the model.

A further limitation of the analysis refers to the accuracy of test sensitivity and specificity differentials between those relatives of genetically negative index cases and those relatives of genetically confirmed index cases. For the purposes of the economic modelling, we have assumed, because of a lack of relevant usable data, that sensitivity and specificity of LDL-C testing in both groups are similar. Although this may overestimate the sensitivity and specificity of LDL-C as a test for relatives of genetically negative index cases, it is justifiable on the basis that all index cases are clinically diagnosed with FH and so may well have genetic mutations that as yet may not have been discovered or have not been detected using any of the tests for this assessment. In terms of the cost-effectiveness results, this could represent a bias of uncertain magnitude in favour of CGA, although in the context of insensitivity to variations in this parameter in probabilistic analysis it is unlikely to alter overall results and conclusions.

Uncertainties

Although the cost-effectiveness analysis was performed using the best available data, there was nonetheless some uncertainty surrounding some of the parameters used in the model. Current NICE guidelines recommend that cascade testing is undertaken for all relatives of index cases (using targeted sequencing for those genetically identified and LDL-C for those with no genetic test or those with a negative genetic test). As discussed, because of our assumption that similar proportions of relatives test positive on LDL-C regardless of the index case's genetic result, this represents some uncertainty. Other issues of uncertainty reflect the parameters and assumptions varied in the deterministic and probabilistic analysis. Results, however, indicate that, in general, the model is insensitive to a range of plausible changes in structure and parameters.

Chapter 6

Conclusions

Implications for service provision

Based on the available, albeit limited, evidence, Elucigene FH20 and LIPOchip version 10 (designed to detect 189 UK-specific mutations) will detect approximately 44–52% and 78.5%, respectively, of FH-causing mutations that are also detected by CGA amongst people with a clinical diagnosis of FH based on Simon Broome criteria. As targeted tests are designed to detect a limited number of genetic mutations, Elucigene FH20 and LIPOchip cannot detect all cases of FH; therefore, further genetic screening using MLPA and sequencing is still required to give an unequivocal diagnosis of FH. This implies that using these targeted tests alone for diagnosis of probands would miss up to approximately 50% (using Elucigene FH20) and 20% (using LIPOchip version 10) of patients with FH-causing mutations who are at risk of developing CHD. As such, these individuals may not receive appropriate treatment and other members of their extended families will also be missed (as they will not be identified for cascade testing).

Using the LDL-C test (high sensitivity and low specificity) as part of the Simon Broome criteria means that a large number of people will receive a clinical diagnosis of FH who will not have a detectable FH-causing mutation. Hence, using LDL-C alone for the diagnosis of FH may lead to inappropriate treatment. In a small UK cohort, age- and gender-specific LDL-C was shown to perform well in the relatives of homozygous FH probands, suggesting the utility of this test for cascade testing (in the absence of genetic tests) among those with a strong phenotype.

As the Elucigene FH20 and LIPOchip kits are designed to detect targeted gene mutations, the sensitivities of both of the kits are largely dependent upon the prevalence of these specific FH-causing mutations in the population. Sensitivities observed in this assessment may not, therefore, be generalisable to other populations or ethnic groups.

At conventional values of willingness to pay for a QALY, CGA is the most cost-effective method of confirmation of clinical diagnosis of FH among Simon Broome possible or definite FH index cases and for the associated cascade testing of first-, second- and third-degree biological relatives. The associated ICER (relative to current practice – LDL-C) is £1030 per QALY gained. The LIPOchip platform and Elucigene FH20 have an even lower reported point estimate of the ICER but are associated with fewer QALY gains. However, there may be practical and resource issues associated with full-scale implementation of CGA if it is recommended as a test strategy for all. If so, then a judgement is required on whether or not it is ethical to implement cascade testing based on an index test result that is not as accurate as alternative more accurate cost-effective options. In addition, a decision-maker needs to be aware that clinicians may or may not base treatment decisions on the outcome of tests such as Elucigene FH20, which detect only around 44% of cases with a FH-causing mutation; for example, there is the potential for missing cases (especially at-risk relatives who may not show high LDL-C levels when tested but may have a FH-causing mutation). These patients may forgo potentially life-saving treatment if index cases are identified only on the basis of their clinical diagnosis as opposed to their genetic test. This issue does not arise in CGA, for which an unequivocal diagnosis is reported. Should a decision-maker deem CGA too expensive given current NHS budgets, Elucigene FH20 and/or LIPOchip

platform (processed in Spain) could be recommended as cost-effective strategies. Probabilistic sensitivity analysis shows CGA to be associated with a probability of cost-effectiveness that is > 90% at threshold values of willingness to pay of > £5000 per QALY gained. Although some variation exists depending on mutation prevalence rates among varying populations, CGA remains the most likely cost-effective testing strategy when the ultimate goal is the identification and treatment of relatives with FH.

It is likely that there would be significant resource use implications associated with implementing the findings of this assessment. As there are approximately 100,000 people with FH as yet undiagnosed, this will provide a substantial resource burden to already tight NHS budgets; however, costs associated with genetic testing are reducing and will continue to do so with the emergence of next-generation sequencing techniques. Similarly, costs of treatment are also likely to reduce going forward as atorvastatin is due to come off patent in 2011 with an expected retail cost similar to that of generic simvastatin.

Currently, CGA is used as the method of cascade testing of choice in only a small number of centres in the UK. The use of CGA is observed to be funded less often by primary care trusts in England than in other parts of the UK where adoption of the technology as part of current practice is much higher. In England, currently 97% of audited sites have access to dedicated lipid measurement services; however, only 12% have access to a dedicated genetic testing service for FH. As the initial cost of CGA is quite high, less costly tests may appear more attractive; however, a judgement call would be required as to what QALY loss would be acceptable to a decision-maker in order to generate cost savings.

Suggested research priorities

There are a number of potential areas in which further research and data would be useful.

- The test performance results of the UK version of LIPOchip were hypothetical and were derived based on a small sample size from one centre where subjects had all been tested genetically. There was no evidence on the performance of LIPOchip version 10 across different regions of the UK or in different ethnic groups. Limited evidence was identified on the sensitivity of Elucigene FH20 across different regions of the UK and in different ethnic groups. As the UK has a population with a wide mutational spectrum, the sensitivity observed with these tests in different populations may vary. Therefore, a prospective multicentre study comparing the performance of Elucigene FH20 and LIPOchip with the LDL-C test in patients with a clinical diagnosis of FH based on the Simon Broome criteria, in which both test-positives and test-negatives are verified against a reference standard of CGA, would be informative. Such a study should also include subgroup analysis of the performance of the tests in different ethnic groups, if possible have a period of follow-up to allow provision of relevant longer-term clinical effectiveness outcomes and incorporate an economic evaluation. The economic evaluation should aim to include a measure of utility of diagnostic information, (especially in relation to the impact of false-negative or false-positive test results on quality-of-life estimates). Such information could be used to assess the impact on QALYs of future modelling exercises.
- There is little evidence linking efficacy of statins in children to the onset of CHD. Although systematic reviews show that statins are efficacious in lowering cholesterol, we have assumed that this leads to similar reductions in cardiovascular events as in the young adult population group. There is a need to assess the relative risks of onset of disease in this group of patients.
- There are many mutations that may have a varying impact in terms of risk of CHD. Evidence on the effect of these mutations is lacking and is an ongoing area of research. There is a

need for a systematic review of all of the FH-causing mutations currently detectable in the UK population as a whole and in specific ethnic groups and their associated impact on risk of CHD.

- There is a requirement for continuing research into finding new, as yet unknown, FH-causing genetic mutations. As only approximately 30–50% of patients with a clinical diagnosis have a mutation confirmed by genetic diagnosis, it is possible that there are many genetic causes of FH as yet undiscovered. This is an area that is progressing and further research is required to inform and update the positive detection rate of CGA based on ongoing clinical research.
- It was outwith the scope of the review to consider tests such as iPLEX, which may also be used for detecting FH but are not as yet CE marked for this purpose. Therefore, further research into the diagnostic accuracy and cost-effectiveness of this test would be informative.

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Contribution of authors

Pawana Sharma (Research Fellow) and Graham Mowatt (Senior Research Fellow) screened the search results, assessed full-text studies for inclusion and undertook data extraction and quality assessment. Pawana Sharma drafted the chapter reporting the results of the diagnostic accuracy studies. Dwayne Boyers (Research Fellow) undertook the economic modelling and drafted the chapter on cost-effectiveness, along with Mary Kilonzo (Research Fellow) and Paul McNamee (Reader in Health Economics). Zosia Miedzybrodzka (Reader in Medical Genetics) and William Simpson (Consultant Chemical Pathologist) drafted the background chapter and provided expert advice on clinical aspects of the review. Charles Boachie (Statistician) conducted the statistical analysis. Fiona Stewart (Information Specialist) developed and ran the search strategies, obtained papers and formatted the references. All authors assisted in preparing the manuscript and commenting on drafts.

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Appendix 1

Age-specific low-density lipoprotein cholesterol cut-offs for females

LDL-C cut-off (mmol/l)					
Age (years)					
0–14	15–24	25–34	35–44	45–54	55+
5.3	5.3	5.3	5.3	5.3	5.3
5.2	5.2	5.2	5.2	5.2	5.2
5.1	5.1	5.1	5.1	5.1	5.1
5.0	5.0	5.0	5.0	5.0	5.0
4.9	4.9	4.9	4.9	4.9	4.9
4.8	4.8	4.8	4.8	4.8	4.8
4.7	4.7	4.7	4.7	4.7	4.7
4.6	4.6	4.6	4.6	4.6	4.6
4.5	4.5	4.5	4.5	4.5	4.5
4.4	4.4	4.4	4.4	4.4	4.4
4.3	4.3	4.3	4.3	4.3	4.3
4.2	4.2	4.2	4.2	4.2	4.2
4.1	4.1	4.1	4.1	4.1	4.1
4.0	4.0	4.0	4.0	4.0	4.0
3.9	3.9	3.9	3.9	3.9	3.9
3.8	3.8	3.8	3.8	3.8	3.8
3.7	3.7	3.7	3.7	3.7	3.7
3.6	3.6	3.6	3.6	3.6	3.6
3.5	3.5	3.5	3.5	3.5	3.5
3.4	3.4	3.4	3.4	3.4	3.4
3.3	3.3	3.3	3.3	3.3	3.3
3.2	3.2	3.2	3.2	3.2	3.2

Relatives with LDL-C levels in the unshaded zone are likely to have a clinical diagnosis of FH.
The diagnosis of FH for relatives in the lightly shaded zone is uncertain.
Relatives with LDL-C levels in the darker shaded zone are unlikely to have FH.'
[The NICE guideline used the following colour shading in this table: red zone (likely to have a clinical diagnosis of FH); grey zone (diagnosis uncertain; green zone (unlikely to have FH)].
Source: NICE.[1]

Appendix 2

Age-specific low-density lipoprotein cholesterol cut-offs for males

LDL-C cut-off (mmol/l)					
Age (years)					
0–14	15–24	25–34	35–44	45–54	55+
5.3	5.3	5.3	5.3	5.3	5.3
5.2	5.2	5.2	5.2	5.2	5.2
5.1	5.1	5.1	5.1	5.1	5.1
5.0	5.0	5.0	5.0	5.0	5.0
4.9	4.9	4.9	4.9	4.9	4.9
4.8	4.8	4.8	4.8	4.8	4.8
4.7	4.7	4.7	4.7	4.7	4.7
4.6	4.6	4.6	4.6	4.6	4.6
4.5	4.5	4.5	4.5	4.5	4.5
4.4	4.4	4.4	4.4	4.4	4.4
4.3	4.3	4.3	4.3	4.3	4.3
4.2	4.2	4.2	4.2	4.2	4.2
4.1	4.1	4.1	4.1	4.1	4.1
4.0	4.0	4.0	4.0	4.0	4.0
3.9	3.9	3.9	3.9	3.9	3.9
3.8	3.8	3.8	3.8	3.8	3.8
3.7	3.7	3.7	3.7	3.7	3.7
3.6	3.6	3.6	3.6	3.6	3.6
3.5	3.5	3.5	3.5	3.5	3.5
3.4	3.4	3.4	3.4	3.4	3.4
3.3	3.3	3.3	3.3	3.3	3.3
3.2	3.2	3.2	3.2	3.2	3.2
3.1	3.1	3.1	3.1	3.1	3.1
3.0	3.0	3.0	3.0	3.0	3.0

Relatives with LDL-C levels in the unshaded zone are likely to have a clinical diagnosis of FH.
The diagnosis of FH for relatives in the lightly shaded zone is uncertain.
Relatives with LDL-C levels in the darker shaded zone are unlikely to have FH.'
[The NICE guideline used the following colour shading in this table: red zone (likely to have a clinical diagnosis of FH); grey zone (diagnosis uncertain; green zone (unlikely to have FH)].
Source: NICE.[1]

Appendix 3

Search strategy

Diagnostic accuracy and clinical effectiveness

MEDLINE (1948 to Week 1 2011), MEDLINE In-Process & Other Non-Indexed Citations (10 January 2011), EMBASE (1980 to 2011 Week 1)

Ovid multifile search
URL: http://gateway.ovid.com

1. Hyperlipoproteinemia Type II/di
2. familial hypercholesterolemia/di
3. lipochip.tw.
4. elucigene.tw.
5. or/1-4
6. Hyperlipoproteinemia Type II/ use prmz
7. familial hypercholesterolemia/ use emez
8. (autosomal dominant adj5 hypercholesterol?emia).tw.
9. familial hypercholesterol?emia.tw.
10. hyperlipoprotein?emia.tw.
11. (familial adj5 apolipoprotein$).tw.
12. or/6-11
13. exp Genetic Predisposition to Disease/ use prmz
14. Genetic Testing/
15. Gene Amplification/ use prmz
16. exp Gene Amplification/ use emez
17. exp Nucleic Acid Amplification Techniques/ use prmz
18. dna microarray/ use emez
19. sequence analysis/ use emez
20. exp polymerase chain reaction/
21. exp sequence analysis/ use prmz
22. base sequence/ use prmz
23. (dna adj3 test$).tw.
24. gene sequencing.tw.
25. comprehensive genetic analysis.tw.
26. mutation screen$.tw.
27. direct sequencing.tw.
28. fragment analysis.tw.
29. (sanger adj3 (method or sequenc$)).tw.
30. (target$ adj3 gene$ sequenc$).tw.
31. (sequenc$ adj3 analysis).tw.
32. (cascade adj3 (test$ or screen$)).tw.
33. (genetic adj3 (test$ or screen$)).tw.
34. (arms or amplification refractory mutation system).tw.
35. (PCR or polymerase chain reaction).tw.
36. Polymorphism, Single-Stranded Conformational/
37. (sscp or single-stranded conformation polymorphism).tw.

38. (mlpa or Multiplex ligation-dependent probe amplification).tw.
39. (hrm or high resolution melt analysis).tw.
40. (DGGE or denaturing gradient gel electrophoresis).tw.
41. (dhplc or denaturing high performance liquid chromatography).tw.
42. Cholesterol, LDL/ use prmz
43. low density lipoprotein cholesterol/ use emez
44. ldl-c.tw.
45. simon broome.tw.
46. or/13-45
47. 12 and 46
48. "sensitivity and specificity"/
49. roc curve/
50. receiver operating characteristic/ use emez
51. predictive value of tests/
52. diagnostic errors/ use emez
53. false positive reactions/ use prmz
54. false negative reactions/ use prmz
55. diagnostic accuracy/ use emez
56. diagnostic value/ use emez
57. du.fs. use prmz
58. sensitivity.tw.
59. distinguish$.tw.
60. differentiat$.tw.
61. identif$.tw.
62. detect$.tw.
63. diagnos$.tw.
64. (predictive adj4 value$).tw.
65. accura$.tw.
66. comparison.tw.
67. or/48-66
68. 47 and 67
69. exp clinical trial/ use emez
70. randomized controlled trial.pt.
71. controlled clinical trial.pt.
72. randomization/ use emez
73. randomi?ed.ab.
74. randomly.ab.
75. trial.ab.
76. groups.ab.
77. or/69-76
78. exp animals/ not humans/
79. 77 not 78
80. 79 and 47
81. comparative study/ use prmz
82. major clinical study/ use emez
83. controlled study/ use emez
84. clinical trial/ use emez
85. (compare$ or compara$).tw.
86. or/81-85
87. 86 and 47
88. 5 or 68 or 80 or 87
89. remove duplicates from 88

90. limit 89 to yr="2000-current"
91. limit 90 to english language

Science Citation Index (1970 to 10 January 2011), Conference Proceedings Citation Index – Science (1990 to 10 January 2011)

URL: www.isiknowledge.com

#1 TS=hyperlipoprotein*emia
#2 TS=(familial SAME hyperlipid*emia)
#3 TS=familial hypercholesterol*emia
#4 TS=((autosomal dominant) SAME hypercholesterol*emia)
#5 TS=(familial SAME apolipoprotein*)
#6 #5 OR #4 OR #3 OR #2 OR #1
#7 TS=low-density lipoprotein cholesterol
#8 TS=ldl-c
#9 TS=ldl cholesterol
#10 TS=simon broome
#11 TS=gene amplification
#12 TS= (DNA same "sequence analysis")
#13 TS=(genetic SAME (test* or screen*))
#14 TS=(cascade SAME (test* or screen*))
#15 TS=mutation screen*
#16 TS=(#6 AND genetic analysis)
#17 TS=(#6 AND gene sequenc*)
#18 #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7
#19 TS=(elucigene or lipochip)
#20 #18 and #6
#21 TS=(#6 SAME (diagnos* or test* or screen* or identif* or detect* or accura* or false positive or false negative))
#22 TS=(#6 SAME (trial* or random* or comparison or compare or comparative))
#23 #22 OR #21
#24 #23 AND #20
#25 #24 OR #19
#26 #24 OR #19 Refined by: Languages=(ENGLISH)
#27 #24 OR #19 Refined by: Languages=(ENGLISH) AND [excluding] Publication Years=(1999)

BIOSIS (1956 to 10 January 2011)

URL: www.isiknowledge.com

#1 TS=hyperlipoprotein*emia
#2 TS=(familial SAME hyperlipid*emia)
#3 TS=familial hypercholesterol*emia
#4 TS=((autosomal dominant) SAME hypercholesterol*emia)
#5 TS=(familial SAME apolipoprotein*)
#6 #5 OR #4 OR #3 OR #2 OR #1
#7 TS=ldl-c
#8 TS=ldl cholesterol
#9 TS=simon broome
#10 TS=gene amplification
#11 TS= (DNA same "sequence analysis")
#12 TS=(genetic SAME (test* or screen*))

#13 TS=(cascade SAME (test* or screen*))
#14 TS=(#6 AND genetic analysis)
#15 TS=(#6 AND gene sequenc*)
#16 TS=(#6 AND low-density lipoprotein cholesterol)
#17 TS=(#6 AND mutation screen*)
#18 #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7
#19 TS=(elucigene or lipochip)
#20 #18 and #6
#21 TS=(#6 SAME (diagnos* or test* or screen* or identif* or detect* or accura* or false positive or false negative))
#22 TS=(#6 SAME (trial* or random* or comparison or compare or comparative))
#23 #22 OR #21
#24 #23 AND #20
#25 #24 OR #19
#26 #24 OR #19 Refined by: [excluding] Publication Years=(1999 OR 1998) AND Languages=(ENGLISH)

Cochrane Controlled Trials Register, Cochrane Database of Systematic Reviews (The Cochrane Library, Issue 1, 2011)

URL: www.thecochranelibrary.com

#1 MeSH descriptor Hyperlipoproteinemia Type II, this term only with qualifier: DI
#2 Lipochip
#3 Elucigene
#4 #1 or #2 or #3
#5 MeSH descriptor Hyperlipoproteinemia Type II, this term only
#6 MeSH descriptor Hyperlipidemia, Familial Combined, this term only
#7 familial hyperlipid*emia
#8 familial hypercholesterol*emia
#9 #5 or #6 or #7 or #8
#10 MeSH descriptor Genetic Predisposition to Disease explode tree 1
#11 MeSH descriptor Genetic Testing, this term only
#12 MeSH descriptor Gene Amplification, this term only
#13 MeSH descriptor Nucleic Acid Amplification Techniques explode all trees
#14 MeSH descriptor Oligonucleotide Array Sequence Analysis explode tree 4
#15 MeSH descriptor Sequence Analysis, DNA explode all trees
#16 dna near/3 test*
#17 gene sequencing
#18 comprehensive genetic analysis
#19 target* near/3 gene* sequenc*
#20 sequenc* near/3 analysis
#21 cascade near/3 (test* or screen*)
#22 genetic near/3 (test$ or screen*)
#23 arms or “amplification refractory mutation system”
#24 PCR or “polymerase chain reaction”
#25 MeSH descriptor Polymorphism, Single-Stranded Conformational, this term only
#26 sscp or “single-stranded conformation polymorphism”
#27 mlpa or “Multiplex ligation-dependent probe amplification”
#28 MeSH descriptor Cholesterol, LDL, this term only
#29 ldl-c
#30 #10 or #11 or #12 or #13 or #14 or#15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29

#31 (#9 AND #30)
#32 (#4 OR #31)
#33 (#32), from 2000 to 2010

Database of Abstracts of Reviews of Effects, Health Technology Assessment database (January 2011), Centre for Reviews and Dissemination

URL: www.york.ac.uk/inst/crd/

#1 MeSH Hyperlipoproteinemia Type II QUALIFIERS DI
#2 elucigene OR lipochip
#3 #1 or #2
#4 MeSH Hyperlipoproteinemia Type II
#5 familial AND hypercholesterolemia
#6 familial AND hypercholesterolaemia
#7 hyperlipoproteinemia
#8 hyperlipoproteinaemia
#9 familial AND hyperlipidemia
#10 familial AND hyperlipidaemia
#11 #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
#12 #3 or #11 RESTRICT YR 2000 2011

ClinicalTrials.gov (December 2010)

URL: www.clinicaltrials.gov

familial hypercholesterolemia OR familial hypercholesterolaemia OR hyperlipoproteinemia type II OR familial combined hyperlipidemia

CenterWatch (December 2010)

URL: www.centerwatch.com

high cholesterol (hyperlipidemia)

Controlled Trials (December 2010)

URL: www.controlledtrials.com/mrct

familial hypercholesterolaemia OR familial hypercholesterolemia OR hyperlipoproteinemia type II OR hyperlipoproteinaemia type II OR familial combined hyperlipidemia OR familial combined hyperlipidaemia

International Clinical Trials Registry (December 2010)

URL: http://apps.who.int/trialsearch/

familial hypercholesterolaemia OR familial hypercholesterolemia OR hyperlipoproteinemia type II OR familial combined hyperlipidemia

Websites consulted

American Association for Clinical Chemistry (December 2010)

URL: www.aacc.org

2010 annual meeting
2009 annual meeting

American Society of Human Genetics (December 2010)
URL: www.ashg.org

2010 meeting
2009 meeting

Atherosclerosis Supplements (December 2010)
URL: www.sciencedirect.com/science/journal/15675688

78th European Atherosclerosis Society Congress, *Atherosclerosis Supplements* 2010;**11**(2)
XII Brazilian Congress of Atherosclerosis, Brazilian Society of Cardiology, *Atherosclerosis Supplements* 2009;**10**(3)
XV International Symposium on Atherosclerosis, *Atherosclerosis Supplements* 2009;**10**(2)

European Society of Human Genetics (December 2010)
URL: www.eshg.org

European Human Genetics Conference 2010, *European Journal of Human Genetics* 2010;**18**(Suppl. 1)
European Human Genetics Conference 2009
https://www.eshg.org/eshg2009/abstracts.htm.

Fonazione Giovanni Lorenzini (December 2010)
URL: www.lorenzinifoundation.org

4th International Conference of Biomarkers in Chronic Diseases (Diabetes, Obesity and Cardiovascular Diseases) 2010

National Genetics Reference Laboratory (December 2010)
URL: www.ngrl.org.uk/Wessex/tech_meeting10.html

New and Developing Technologies for Genetic Diagnostics '10

Cost-effectiveness

MEDLINE (1948 to Week 4 2011), MEDLINE In-Process & Other Non-Indexed Citations (2 February 2011), EMBASE (1980 to 2011 Week 4)
Ovid multifile search
URL: http://gateway.ovid.com

1. Hyperlipoproteinemia Type II/di [Diagnosis]
2. familial hypercholesterolemia/di
3. lipochip.tw.
4. elucigene.tw.
5. or/1-4
6. Hyperlipoproteinemia Type II/ use prmz
7. familial hypercholesterolemia/ use emez
8. (autosomal dominant adj5 hypercholesterol?emia).tw.
9. familial hypercholesterol?emia.tw.

10. hyperlipoprotein?emia.tw.
11. (familial adj5 apolipoprotein$).tw.
12. or/6-11
13. exp Genetic Predisposition to Disease/ use prmz
14. Genetic Testing/
15. Gene Amplification/ use prmz
16. exp Gene Amplification/ use emez
17. exp Nucleic Acid Amplification Techniques/ use prmz
18. dna microarray/ use emez
19. sequence analysis/ use emez
20. exp polymerase chain reaction/
21. exp sequence analysis/ use prmz
22. base sequence/ use prmz
23. (dna adj3 test$).tw.
24. gene sequencing.tw.
25. comprehensive genetic analysis.tw.
26. mutation screen$.tw.
27. direct sequencing.tw.
28. fragment analysis.tw.
29. (sanger adj3 (method or sequenc$)).tw.
30. (target$ adj3 gene$ sequenc$).tw.
31. (sequenc$ adj3 analysis).tw.
32. (cascade adj3 (test$ or screen$)).tw.
33. (genetic adj3 (test$ or screen$)).tw.
34. (arms or amplification refractory mutation system).tw.
35. (PCR or polymerase chain reaction).tw.
36. Polymorphism, Single-Stranded Conformational/
37. (sscp or single-stranded conformation polymorphism).tw.
38. (mlpa or Multiplex ligation-dependent probe amplification).tw.
39. (hrm or high resolution melt analysis).tw.
40. (DGGE or denaturing gradient gel electrophoresis).tw.
41. (dhplc or denaturing high performance liquid chromatography).tw.
42. Cholesterol, LDL/ use prmz
43. low density lipoprotein cholesterol/ use emez
44. ldl-c.tw.
45. simon broome.tw.
46. or/13-45
47. 12 and 5 and 46
48. exp "costs and cost analysis"/ use prmz
49. economics/
50. exp economic evaluation/ use emez
51. exp models, economic/
52. exp decision theory/
53. ec.fs.
54. monte carlo method/
55. markov chains/
56. exp health status indicators/
57. cost$.ti.
58. (cost$ adj2 (effective$ or utilit$ or benefit$ or minimis$)).ab.
59. economic$ model$.tw.

60. (price$ or pricing).tw.
61. (financial or finance or finances or financed).tw.
62. markov$.tw.
63. monte carlo.tw.
64. (decision$ adj2 (tree? or analy$ or model$)).tw.
65. (standard adj1 gamble).tw.
66. trade off.tw.
67. or/48-66
68. 47 and 67
69. limit 68 to yr="2000 -Current"
70. limit 69 to english language
71. remove duplicates from 70

Science Citation Index (1970 to 2 February 2011), Conference Proceedings Citation Index – Science (1990 to 2 February 2011)

URL: www.isiknowledge.com

#1 TS=hyperlipoprotein*emia
#2 TS=(familial SAME hyperlipid*emia)
#3 TS=familial hypercholesterol*emia
#4 TS=((autosomal dominant) SAME hypercholesterol*emia)
#5 TS=(familial SAME apolipoprotein*)
#6 #5 OR #4 OR #3 OR #2 OR #1
#7 TS=low-density lipoprotein cholesterol
#8 TS=ldl-c
#9 TS=ldl cholesterol
#10 TS=simon broome
#11 TS=gene amplification
#12 TS= (DNA same "sequence analysis")
#13 TS=(genetic SAME (test* or screen*))
#14 TS=(cascade SAME (test* or screen*))
#15 TS=mutation screen*
#16 TS=(#6 AND genetic analysis)
#17 TS=(#6 AND gene sequenc*)
#18 #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7
#19 TS=(elucigene or lipochip)
#20 #18 and #6
#21 TS=(#20 AND economic*)
#22 TS=(#20 AND cost*)
#23 TS=(#20 AND price*)
#24 TS=(#20 AND pricing*)
#25 TS=(#20 AND financ*)
#26 TS=(#20 AND markov*)
#27 TS=(#20 AND monte carlo)
#28 TS=(decision SAME (tree* OR analy* OR model*))
#29 #28 OR #27 OR #26 OR #25 OR #24 OR #23 OR #22 OR #21
#30 #29 AND #20
#31 #30 OR #19
#32 #30 OR #19 Refined by: Languages=(ENGLISH) AND [excluding] Publication Years=(1999)

NHS Economic Evaluation Database (February 2011), Centre for Reviews and Dissemination

URL: www.york.ac.uk/inst/crd/

#1	MeSH Hyperlipoproteinemia Type II QUALIFIERS DI
#2	elucigene OR lipochip
#3	#1 or #2
#4	MeSH Hyperlipoproteinemia Type II
#5	familial AND hypercholesterolemia
#6	familial AND hypercholesterolaemia
#7	hyperlipoproteinemia
#8	hyperlipoproteinaemia
#9	familial AND hyperlipidemia
#10	familial AND hyperlipidaemia
#11	#3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
#12	#3 or #11 RESTRICT YR 2000 2011

Cost-effectiveness Analysis Registry (February 2011)

URL: https://research.tufts-nemc.org/cear4/default.aspx
Search terms: familial hypercholesterolaemia OR familial hypercholesterolemia

Quality-of-life and cost data for model

MEDLINE (1948 to Week 4 2011), MEDLINE In-Process & Other Non-Indexed Citations (2 February 2011), EMBASE (1980 to 2011 Week 4)

Ovid multifile search
URL: http://gateway.ovid.com

1. Hyperlipoproteinemia Type II/di [Diagnosis]
2. familial hypercholesterolemia/di
3. lipochip.tw.
4. elucigene.tw.
5. or/1-4
6. Hyperlipoproteinemia Type II/ use prmz
7. familial hypercholesterolemia/ use emez
8. (autosomal dominant adj5 hypercholesterol?emia).tw.
9. familial hypercholesterol?emia.tw.
10. hyperlipoprotein?emia.tw.
11. (familial adj5 apolipoprotein$).tw.
12. or/6-11
13. exp Genetic Predisposition to Disease/ use prmz
14. Genetic Testing/
15. Gene Amplification/ use prmz
16. exp Gene Amplification/ use emez
17. exp Nucleic Acid Amplification Techniques/ use prmz
18. dna microarray/ use emez
19. sequence analysis/ use emez
20. exp polymerase chain reaction/
21. exp sequence analysis/ use prmz

22. base sequence/ use prmz
23. (dna adj3 test$).tw.
24. gene sequencing.tw.
25. comprehensive genetic analysis.tw.
26. mutation screen$.tw.
27. direct sequencing.tw.
28. fragment analysis.tw.
29. (sanger adj3 (method or sequenc$)).tw.
30. (target$ adj3 gene$ sequenc$).tw.
31. (sequenc$ adj3 analysis).tw.
32. (cascade adj3 (test$ or screen$)).tw.
33. (genetic adj3 (test$ or screen$)).tw.
34. (arms or amplification refractory mutation system).tw.
35. (PCR or polymerase chain reaction).tw.
36. Polymorphism, Single-Stranded Conformational/
37. (sscp or single-stranded conformation polymorphism).tw.
38. (mlpa or Multiplex ligation-dependent probe amplification).tw.
39. (hrm or high resolution melt analysis).tw.
40. (DGGE or denaturing gradient gel electrophoresis).tw.
41. (dhplc or denaturing high performance liquid chromatography).tw.
42. Cholesterol, LDL/ use prmz
43. low density lipoprotein cholesterol/ use emez
44. ldl-c.tw.
45. simon broome.tw.
46. or/13-45
47. 5 and 12 and 46
48. quality of life/
49. quality adjusted life year/
50. "Value of Life"/ use prmz
51. health status indicators/ use prmz
52. health status/ use emez
53. sickness impact profile/ use prmz
54. disability evaluation/ use prmz
55. disability/ use emez
56. activities of daily living/ use prmz
57. exp daily life activity/ use emez
58. cost utility analysis/ use emez
59. rating scale/
60. questionnaires/
61. (quality adj1 life).tw.
62. quality adjusted life.tw.
63. disability adjusted life.tw.
64. (qaly? or qald? or qale? or qtime? or daly?).tw.
65. (euroqol or euro qol or eq5d or eq 5d).tw.
66. (hql or hqol or h qol or hrqol or hr qol).tw.
67. (hye or hyes).tw.
68. health$ year$ equivalent$.tw.
69. (hui or hui1 or hui2 or hui3).tw.
70. (health adj3 (utilit$ or disutili$)).tw.
71. (health adj3 (state or status)).tw.
72. (sf36 or sf 36 or short form 36 or shortform 36).tw.
73. (sf6 or sf 6 or short form 6 or shortform 6).tw.

74. (sf12 or sf 12 or short form 12 or shortform 12).tw.
75. (sf16 or sf 16 or short form 16 or shortform 16).tw.
76. (sf20 or sf 20 or short form 20 or shortform 20).tw.
77. willingness to pay.tw.
78. standard gamble.tw.
79. trade off.tw.
80. conjoint analys?s.tw.
81. discrete choice.tw.
82. or/48-81
83. 47 and 82
84. limit 83 to yr="2000-current"
85. limit 84 to english language

IDEAS (February 2011)

URL: http://ideas.repec.org/

Efficacy of statins

MEDLINE (1948 to Week 9 2011), MEDLINE In-Process & Other Non-Indexed Citations (9 March 2011), EMBASE (1980 to 2011 Week 9)

Ovid multifile search
URL: http://gateway.ovid.com

1. Hyperlipoproteinemia Type II/ use prmz
2. familial hypercholesterolemia/ use emez
3. (autosomal dominant adj5 hypercholesterol?emia).tw.
4. familial hypercholesterol?emia.tw.
5. hyperlipoprotein?emia.tw.
6. (familial adj5 apolipoprotein$).tw.
7. or/1-6
8. exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/ use prmz
9. hydroxymethylglutaryl coenzyme A reductase inhibitor/ use emez
10. Simvastatin/
11. Pravastatin/
12. rosuvastatin/ use emez
13. fluindostatin/ use emez
14. atorvastatin/ use emez
15. (simvastatin or pravastatin or rosuvastatin or fluvastatin or atorvastatin or statin$).tw.
16. hmg-coa.tw.
17. or/8-12
18. 7 and 17
19. exp animals/ not humans/
20. 18 not 19
21. limit 20 to yr="2008-current"
22. 2008$.ed.
23. 2008$.em.
24. 22 or 23
25. 20 and 24
26. 21 or 25
27. (letter or comment or editorial).pt.
28. 26 not 27

29. remove duplicates from 28
30. limit 29 to english language
31. limit 28 to yr="2000-current"

Database of Abstracts of Reviews of Effects, NHS Economic Evaluation Database, Health Technology Assessment database (March 2011), Centre for Reviews and Dissemination

URL: www.york.ac.uk/inst/crd/

#1 MeSH Hyperlipoproteinemia Type II
#2 familial AND hypercholesterolemia
#3 familial AND hypercholesterolaemia
#4 hyperlipoproteinemia
#5 hyperlipoproteinaemia
#6 familial AND hyperlipidemia
#7 familial AND hyperlipidaemia
#8 #1 or #2 or #3 or #4 or #5 or #6 or #7
#9 MeSH Hydroxymethylglutaryl-CoA Reductase Inhibitors
#10 MeSH Simvastatin
#11 MeSH Pravastatin
#12 simvastatin OR pravastatin OR rosuvastatin OR fluvastatin OR atorvastatin OR statin*
#13 hmg-coa
#14 #9 or #10 or #11 or #12 or #13
#15 #8 and #14 RESTRICT YR 2000 2011

Cochrane Database of Systematic Reviews (The Cochrane Library, Issue 3, 2011)

URL: www.thecochranelibrary.com

#1 MeSH descriptor Hyperlipoproteinemia Type II, this term only
#2 MeSH descriptor Hyperlipidemia, Familial Combined, this term only
#3 familial hyperlipid*emia
#4 familial hypercholesterol*emia
#5 (#1 OR #2 OR #3 OR #4)
#6 MeSH descriptor Hydroxymethylglutaryl-CoA Reductase Inhibitors explode tree 1
#7 MeSH descriptor Simvastatin, this term only
#8 MeSH descriptor Pravastatin, this term only
#9 simvastatin OR pravastatin OR rosuvastatin OR fluvastatin OR atorvastatin OR statin*
#10 hmg-coa
#11 (#6 OR #7 OR #8 OR #9 OR #10)
#12 (#5 AND #11), from 2007 to 2011

Effect of mutation type on treatment choice

MEDLINE (1948 to March Week 1 2011), MEDLINE In-Process & Other Non-Indexed Citations (14 March 2011), EMBASE (1980 to 2011 Week 10)

Ovid multifile search
URL: http://gateway.ovid.com

1. Hyperlipoproteinemia Type II/ use prmz
2. familial hypercholesterolemia/ use emez

3. (autosomal dominant adj5 hypercholesterol?emia).tw.
4. familial hypercholesterol?emia.tw.
5. hyperlipoprotein?emia.tw.
6. (familial adj5 apolipoprotein$).tw.
7. or/1-6
8. Hyperlipoproteinemia Type II/dt [Drug Therapy]
9. familial hypercholesterolemia/dt [Drug Therapy]
10. or/8-9
11. exp Mutation/
12. (mutation$ adj2 variation$).tw.
13. (mutation$ adj2 type$).tw.
14. or/11-13
15. Niacin/ use prmz
16. nicotinic acid/ use emez
17. (niacin or nicotonic acid).tw.
18. exp Fibric Acids/ use prmz
19. exp fibric acid derivative/ use emez
20. fibrate$.tw.
21. exp Fish Oils/ use prmz
22. fish oil/ use emez
23. omega 3 fatty acid/ use emez
24. fish oil$.tw.
25. omega 3.tw.
26. exp Blood Component Removal/ use prmz
27. exp apheresis/ use emez
28. (aphersis or plasmapheresis).tw.
29. resin/ use emez
30. resin$.tw.
31. ezetimibe/ use emez
32. ezetimibe.tw.
33. or/15-32
34. 10 and 14
35. 7 and 14 and 33
36. 34 or 35
37. (comment or letter or editorial).pt.
38. 36 not 37
39. limit 36 to english language
40. limit 39 to yr="2000 -Current"
41. remove duplicates from 40

Cochrane Database of Systematic Reviews (The Cochrane Library, Issue 3, 2011)

URL: www.thecochranelibrary.com

#1 MeSH descriptor Hyperlipoproteinemia Type II, this term only
#2 MeSH descriptor Hyperlipidemia, Familial Combined, this term only
#3 familial hyperlipid*emia
#4 familial hypercholesterol*emia
#5 (#1 OR #2 OR #3 OR #4)
#6 MeSH descriptor Hyperlipoproteinemia Type II, this term only with qualifier: DT
#7 MeSH descriptor Mutation explode all trees
#8 mutation* variation*

#9 mutation* type*
#10 (#7 OR #8 OR #9)
#11 (#5 AND #10)
#12 (#6 AND #10)
#13 (#11 OR #12)

Database of Abstracts of Reviews of Effects, NHS Economic Evaluation Database, Health Technology Assessment database (March 2011), Centre for Reviews and Dissemination

URL: www.york.ac.uk/inst/crd/

#1 MeSH Hyperlipoproteinemia Type II
#2 familial AND hypercholesterolemia
#3 familial AND hypercholesterolaemia
#4 familial AND hyperlipidemia
#5 familial AND hyperlipidaemia
#6 #1 #2 or #3 or #4 or #5
#7 MeSH Hyperlipoproteinemia Type II QUALIFIERS DT
#8 MeSH Mutation EXPLODE 1
#9 mutation* AND type*
#10 mutation* AND variation*
#11 #8 or #9 or #10
#12 #6 and #11
#13 #7 or #12

Utility of diagnostic information

MEDLINE (1996 to February Week 4 2011)

Ovid multifile search
URL: http://gateway.ovid.com

1. *genetic testing/
2. *quality of life/px
3. *psychology/
4. *patient satisfaction/
5. *patient acceptance of health care/
6. *attitude to health/
7. *rating scale/
8. *questionnaires/
9. (quality adj1 life).tw
10. (patient? adj1 (preferenc$ or experienc$ or perception$ or satisfaction$)).ti.
11. quality of life/
12. quality adjusted life year/
13. "Value of Life"/
14. health status indicators/
15. sickness impact profile/
16. quality adjusted life.tw.
17. disability adjusted life.tw.
18. (qaly? or qald? or qale? or qtime? or daly?).tw.
19. (euroqol or euro qol or eq5d or eq 5d).tw
20. (hql or hqol or h qol or hrqol or hr qol).tw.

21. (hye or hyes).tw
22. health$ year$ equivalent$.tw
23. (hui or hui1 or hui2 or hui3).tw.
24. (health adj3 (utilit$ or disutili$)).tw.
25. (health adj3 (state or status)).tw.
26. (sf36 or sf 36 or short form 36 or shortform 36).tw.
27. (sf6 or sf 6 or short form 6 or shortform 6).tw.
28. (sf12 or sf 12 or short form 12 or shortform 12).tw.
29. (sf16 or sf 16 or short form 16 or shortform 16).tw.
30. (sf20 or sf 20 or short form 20 or shortform 20).tw.
31. willingness to pay.tw.
32. standard gamble.tw.
33. trade off.tw.
34. conjoint analys?s.tw.
35. discrete choice.tw.
36. or/2-35
37. 1 and 36
38. limit 37 to (english language and yr="2000 -Current")

Database of Abstracts of Reviews of Effects, NHS Economic Evaluation Database, Health Technology Assessment database (March 2011), Centre for Reviews and Dissemination

URL: www.york.ac.uk/inst/crd/

#1 MeSH Genetic Screening EXPLODE 1 2 3 4 5 6 7 RESTRICT YR 2000 2011
#2 cost:ty
#3 #1 NOT #2

Appendix 4

Data extraction form

Elucigene FH20 and LIPOchip for FH - data extraction form

Reviewer ID: Date:

Administration details

Study ID: Publication status:

Other papers this study may link with:

Aim of the study

Test(s) reported

	Index cases	Cascade testing
Elucigene	☐	☐
LIPOchip	☐	☐
LDL-C	☐	☐
Targeted gene sequencing		☐
*CGA	☐	☐

* includes DNA sequence analysis+ test for deletion/duplication+ analysis of APOB p.Arg3527Gln and PCSK9 p.Asp374Tyr using various techniques.

Outcomes reported

Diagnostic accuracy ☐ Mutation detection rate ☐ Clinical effectiveness ☐

Study details

Cross-sectional comparative ☐ RCT ☐ Case control study ☐

Cross-sectional single test ☐ Other, please specify: ☐

Multicentre study? Yes ☐ No ☐ If Yes, number of centres:

Consecutive recruitment? Yes ☐ No ☐ Not stated ☐

Country:

Study dates:

Length of follow up:

Source of funding:

Inclusion criteria:

Exclusion criteria:

Baseline characteristics of participants

Adults ☐ Children ☐

Criteria used for clinical diagnosis:

Simon Broome ☐

Dutch ☐

Medped ☐

Other ☐ specify the LDLC cut offs used and definition

Type of FH:

Possible ☐ Unclassified FH ☐

Definite ☐ Not stated ☐

Heterozygous FH ☐ Homozygous FH ☐

Diagnosis of the Index cases confirmed by:

Clinical test ☐ Genetic test ☐

Who perform the clinical diagnosis?

Number of participant/sample

give detail of each type of FH if reported	All	Index cases	Relatives
Eligible			

Enrolled			
Analysed			
Received index test(s)			
Received comparator test(s) for index cases			
Received cascade test(s) 1st degree relatives 2nd degree relatives 3rd degree relatives			
Received comparator test(s) 1st degree relatives 2nd degree relatives 3rd degree relatives			
Age (mean/ median, SD, range)			
Receiving treatment for hyper- cholestorelaemia (specify treatment)			
Ethnicity			
Gender	**M:** **F:**	**M:** **F:**	**M:** **F:**
Tendon xanthomas			
Coronary Heart Disease			

Intervention tests

Elucigene FH20 (Tepnel molecular diagnostics)

If not FH20 which version and how many mutations was it designed to detect?

Gel-based analysis ☐ Fluorescent analysis: ☐

Who carried out the test?

Where was the test undertaken?

Time taken to obtain test results:

Additional information on the test:

LIPOchip (Progenika Biopharma)

If not version 10 which version and how many mutations was it designed to detect?

Samples processed at: LIPOchip laboratory ☐ Other ☐ If other, please give details:

Methodology used:

DNA array ☐

Analysis for large gene re-arrangements ☐

Automated sequencing of the LDLR ☐

Who carried out the test?

Where was the test undertaken?

Time taken to obtain test results:

Additional information on the test:

Comparator tests

CGA (as defined on page 5 of the protocol)

CGA should include following:

☐ DNA sequence analysis of the promoter, all exons, the exon/intron boundaries and into 3' untranslated region of the LDLR gene

Manufacturer and any other technical characteristics of the test:

☐ MLPA for each exon and the promoter region of the LDLR gene to detect deletions and duplications

Manufacturer and any other technical characteristics of the test:

☐ Analysis for the common APOB p.Arg3527Gin and PCSK9 p.Asp374Tyr gene mutations

Manufacturer and any other technical characteristics of the test:

Who carried out the test?

Where was the test undertaken?

Time taken to obtain test results:

Additional information on the test:

LDL-C concentration

Estimated from a fasting blood sample using the Friedwald equation? Yes ☐ No ☐

If No please specify method used:

For cascade test please specify age and gender specific LDL-C cut offs:

No. of times LDL-C was measured? Once ☐ Twice ☐ Not stated ☐

Criteria used to define a positive test result:

Who carried out the test?

Where was the test undertaken?

Time taken to obtain test results:

Additional information on the test:

If targeted gene sequencing of relatives was undertaken, please give details:

Reference standard test

Was there a reference standard test that consisted of either of the followings?

CGA in combination with Simon Broome criteria ☐

CGA only ☐

Simon Broome only ☐

Results for Index cases

1. Genetic test ……..

	LDLR	*APOB*	*PCSK9*	*MLPA*	*sequencing*	*Total*
Number of participants						
Number of samples analysed						
n/N (%) with mutation detected						
n/N (%) with no mutation detected						

2. Genetic test ……..

Number of participants						
Number of samples analysed						
n/N (%) with mutation detected						
n/N (%) with no mutation detected						

3. LDL-C as a clinical test						
Number of participants						
Number of samples analysed						
Number of FH diagnosed						
Number of FH not diagnosed						
Results for Cascade test						
Specify the genetic test……..						
Number of participants (Index cases)						
Number of samples analysed						
Number of families tested						
n/N (%) with mutation detected						
n/N (%) with no mutation detected						
LDL-C age and sex specific test						
Number of participants (Index cases)						
Number of samples analysed						
Number of families tested						
Number of FH diagnosed						
Number of FH not diagnosed						
Record data on each level of analysis containing 2x2 tables of true and false positives and negatives for **Test accuracy of genetic test (Elucigene/Lipochip) vs genetic test (CGA)** **Test accuracy of genetic test (Elucigene/Lipochip) vs clinical test (LDL-C-SB criteria)**						

Subgroup analysis reported (e.g. ethnicity)? Yes ☐ No ☐ If Yes please give details:
Give details of any clinical effectiveness outcomes reported, e.g. cholesterol levels following treatment, CHD events etc or probability of true FH:
Give details of any information reported on acceptability and/or interpretability of the tests
Additional information:

Appendix 5

Modified QUADAS checklist

Item		Yes	No	Unclear
1	Was the spectrum of patients representative of the patients who will receive the test in practice?			
2	Is the reference standard likely to correctly classify the target condition?[a]			
3	Did the whole sample or a random selection of the sample receive verification using a reference standard of diagnosis?			
4	Did patients receive the same reference standard regardless of the index test result?			
5	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?			
6	Were the index test results interpreted without knowledge of the results of the reference standard?			
7	Were the reference standard results interpreted without knowledge of the results of the index test?			
8	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?[b]			
9	Were uninterpretable/intermediate/test results reported?			
10	Were withdrawals from the study explained?			
11	Were cut-off values established before the study was started?			
12	Is the technology of the index test unchanged since the study was carried out?			
13	Did the study provide a clear definition of what was considered to be a 'positive' result?[c]			

a 'Yes' if studies reported the following: (1) DNA sequence analysis of the promoter, all exons, the exon/intron boundaries and into the 3′ untranslated region of the *LDLR* gene; (2) MLPA for each exon and the promoter region of the *LDLR* gene to detect deletions and duplications; and (3) *APOB* analysis.
b 'Yes' if studies reporting on clinical diagnosis also include personal and family history of cardiovascular diseases and hyperlipidaemia.
c For FH diagnosed clinically only.

Please also note if the paper reported details of any of the following issues:

- MLPA: the location of probes in the intron; single nucleotide polymorphism (SNP) at probe binding site
- Elucigene FH20: inadequate electrophoretic separation and misidentification of the FH20 mutations
- LIPOchip: assessment of batch capacity; assessment of training requirements; assessment of instrumentation required, maintenance, etc.

Appendix 6

List of included studies

Alonso 2009

Alonso R, Defesche JC, Tejedor D, Castillo S, Stef M, Mata N, *et al.* Genetic diagnosis of familial hypercholesterolemia using a DNA-array based platform. *Clin Biochem* 2009;**42**:899–903.

Callaway 2010

Callaway J, Wood O, Cross E, Skinner AC, Harvey JF. Validation of a novel mutation screening strategy for familial hypercholesterolaemia LIPOchip, a DNA-array based system. *J Med Genet* 2010;**47**:S62.

Civeira 2008

Civeira F, Ros E, Jarauta E, Plana N, Zambon D, Puzo J, *et al.* Comparison of genetic versus clinical diagnosis in familial hypercholesterolemia. *Am J Cardiol* 2008;**102**:1187–93.

Damgaard 2005

Damgaard D, Larsen ML, Nissen PH, Jensen JM, Jensen HK, Soerensen VR, *et al.* The relationship of molecular genetic to clinical diagnosis of familial hypercholesterolemia in a Danish population. *Atherosclerosis* 2005;**180**:155–60.

Hooper 2009

Hooper AJ, Nguyen LT, Burnett JR, Van Bockxmeer FM. Molecular screening approach for identification of mutations causing familial hypercholesterolaemia in Western Australia. *Twin Res Hum Genet* 2009;**12**:218.

Lee 2010

Lee WP, Ong BB, Haralambos K, Townsend D, Rees JAE, Williams EJ, *et al.* Familial hypercholesterolaemia screening – application of genetic testing and diagnostic LDL-C cut-off values for relatives of FH patients in a Welsh population. *Eur Heart J Suppl* 2010;**12**:F20–1.

Mabuchi 2005

Mabuchi H, Higashikata T, Nohara A, Lu H, Yu WX, Nozue T, *et al.* Cutoff point separating affected and unaffected familial hypercholesterolemic patients validated by LDL-receptor gene mutants. *J Atheroscler Thromb* 2005;**12**:35–40.

Palacios 2010

Primary study

Palacios L, Stef M, Taylor A, Humphries SE, Cuevas N, McAnulty C, *et al.* Rapid and accurate genetic diagnosis by LIPOchip (R) in UK FH patients. *Atheroscler Suppl* 2010;**11**:31.

Secondary study

Stef M. *Rapid diagnosis of familial hypercholesterolemia in British patients.* New and Developing Technologies for Genetic Diagnostics, Salisbury, 5–6 July 2010. URL: www.ngrl.org.uk/Wessex/downloads/tm10/TM10-S2-2%20Marianne%20Stef.pdf (accessed March 2011).

Starr 2008

Starr B, Hadfield SG, Hutten BA, Lansberg PJ, Leren TP, Damgaard D, *et al.* 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. *Clin Chem Lab Med* 2008;**46**:791–803.

Stef 2009

Stef M, Palacios L, Tejedor D, Martinez A. The LIPOchip experience in Spain. *Atheroscler Suppl* 2009;**10**:e1001.

Taylor 2010

Primary study

Taylor A, Wang D, Patel K, Whittall R, Wood G, Farrer M, *et al.* Mutation detection rate and spectrum in familial hypercholesterolaemia patients in the UK pilot cascade project. *Clin Genet* 2010;**77**:572–80.

Secondary study

Taylor A, Tabrah S, Wang D, Sozen M, Duxbury N, Whittall R, *et al.* Multiplex ARMS analysis to detect 13 common mutations in familial hypercholesterolaemia. *Clin Genet* 2007;**71**:561–8.

Tejedor 2005

Tejedor D, Castillo S, Mozas P, Jimenez E, Lopez M, Tejedor MT, *et al.* Reliable low-density DNA array based on allele-specific probes for detection of 118 mutations causing familial hypercholesterolemia. *Clin Chem* 2005;**51**:1137–44.

Widham 2007

Widhalm K, Dirisamer A, Lindemayr A, Kostner G. Diagnosis of families with familial hypercholesterolaemia and/or Apo B-100 defect by means of DNA analysis of LDL-receptor gene mutations. *J Inherit Metab Dis* 2007;**30**:239–47.

Wiegman 2003

Wiegman A, Rodenburg J, De Jongh S, Defesche JC, Bakker HD, Kastelein JJP, *et al.* Family history and cardiovascular risk in familial hypercholesterolemia: data in more than 1000 children. *Circulation* 2003;**107**:1473–8.

Yarram 2010

Yarram L. *Familial hypercholesterolaemia: LIPOchip experience.* Clinical Molecular Genetics Society meeting, St Catherine's College, Oxford, April 2010. URL: www.cmgs.org/Restricted%20access%20area/CMGS%20members/CMGS%202010/SP1_5/SP01%20FH%20Lipochip%20experience%20CMGS.ppt (accessed April 2011).

Appendix 7

List of excluded studies

Not a required reference standard (*APOB* or *PCSK9* or deletion/duplication only)

Cantafora A, Blotta I, Pino E, Pisciotta L, Calandra S, Bertolini S. Quantitative polymerase chain reaction and microchip electrophoresis to detect major rearrangements of the low-density lipoprotein receptor gene causing familial hypercholesterolemia. *Electrophoresis* 2004;**25**:3882–9.

Garcia-Garcia AB, Blesa S, Martinez-Hervas S, Mansego ML, Gonzalez-Albert V, Ascaso JF, *et al.* Semiquantitative multiplex PCR: a useful tool for large rearrangement screening and characterization. *Hum Mutat* 2006;**27**:822–8.

Garcia-Otin AL, Strunk M, Pueyo M, Solanas M, Fiddyment S, Aceves M, *et al.* Screening for PCSK9 mutations in Spanish patients with autosomal dominant hypercholesterolemia unrelated to LDLR or APOB. *Atheroscler Suppl* 2009;**10**:e1228.

Goldmann R, Tichy L, Freiberger T, Zapletalova P, Letocha O, Soska V, *et al.* Genomic characterization of large rearrangements of the LDLR gene in Czech patients with familial hypercholesterolemia. *BMC Med Genet* 2010;**11**:115.

Heath KE, Day INM, Humphries SE. Universal primer quantitative fluorescent multiplex (UPQFM) PCR: a method to detect major and minor rearrangements of the low density lipoprotein receptor gene. *J Med Genet* 2000;**37**:272–80.

Holla OL, Teie C, Berge KE, Leren TP. Identification of deletions and duplications in the low density lipoprotein receptor gene by MLPA. *Clin Chim Acta* 2005;**356**:164–71.

Kalina A, Csaszar A, Czeizel AE, Romics L, Szaboki F, Szalai C, *et al.* Frequency of the R3500Q mutation of the apolipoprotein B-100 gene in a sample screened clinically for familial hypercholesterolemia in Hungary. *Atherosclerosis* 2001;**154**:247–51.

Liyanage KE, Hooper AJ, Defesche JC, Burnett JR, Van Bockxmeer FM. High-resolution melting analysis for detection of familial ligand-defective apolipoprotein B-100 mutations. *Ann Clin Biochem* 2008;**45**:170–6.

Merino-Ibarra E, Castillo S, Mozas P, Cenarro A, Martorell E, Diaz JL, *et al.* Screening of APOB gene mutations in subjects with clinical diagnosis of familial hypercholesterolemia. *Hum Biol* 2005;**77**:663–73.

Meshkov A, Stambolsky D, Malyshev P, Kotkina T, Boitsov S, Kukharchuk V. The prevalence of apolipoprotein B-100 gene mutations in Russian familial hypercholesterolemia patients. *Atheroscler Suppl* 2009;**10**:e990.

Taylor A, Martin B, Wang D, Patel K, Humphries SE, Norbury G. Multiplex ligation-dependent probe amplification analysis to screen for deletions and duplications of the LDLR gene in patients with familial hypercholesterolaemia. *Clin Genet* 2009;**76**:69–75.

Case report

Taylor A, Bayly G, Patel K, Yarram L, Williams M, Hamilton-Shield J, *et al.* A double heterozygote for familial hypercholesterolaemia and familial defective apolipoprotein B-100. *Ann Clin Biochem* 2010;**47**:5–90.

Single test (comprehensive genetic analysis) or insufficient/not usable data to allow calculation of test performance

Alonso R, Mata N, Castillo S, Fuentes F, Saenz P, Muniz O, *et al.* Cardiovascular disease in familial hypercholesterolaemia: influence of low-density lipoprotein receptor mutation type and classic risk factors. *Atherosclerosis* 2008;**200**:315–21.

Alves A, Medeiros A, Francisco V, Bourbon M. Familial hypercholesterolaemia: a perspective of 10 years of study in Portugal. *Atherosclerosis* 2009;**10**:e1219.

Alves AC, Medeiros AM, Francisco V, Gaspar IM, Rato Q, Bourbon M. Molecular diagnosis of familial hypercholesterolemia: an important tool for cardiovascular risk stratification. *Rev Port Cardiol* 2010;**29**:907–21.

Arraiz N, Bermudez V, Rondon N, Reyes F, Borjas L, Solis E, *et al.* Novel mutations identification in exon 4 of LDLR gene in patients with moderate hypercholesterolemia in a Venezuelan population. *Am J Ther* 2010;**17**:325–9.

Bertolini S, Cantafora A, Averna M, Cortese C, Motti C, Martini S, *et al.* Clinical expression of familial hypercholesterolemia in clusters of mutations of the LDL receptor gene that cause a receptor-defective or receptor-negative phenotype. *Arterioscler Thromb Vasc Biol* 2000;**20**:E41–52.

Bhatnagar D, Morgan J, Siddiq S, Mackness MI, Miller JP, Durrington PN. Outcome of case finding among relatives of patients with known heterozygous familial hypercholesterolaemia. *BMJ* 2000;**321**:1497–500.

Blesa S, Garcia-Garcia AB, Martinez-Hervas S, Mansego ML, Gonzalez-Albert V, Ascaso JF, *et al.* Analysis of sequence variations in the LDL receptor gene in Spain: general gene screening or search for specific alterations? *Clin Chem* 2006;**52**:1021–5.

Bourbon M, Rato Q. Portuguese familial hypercholesterolemia study: presentation of the study and preliminary results. *Rev Port Cardiol* 2006;**25**:999–1013.

Bourbon M, Alves AC, Medeiros AM, Silva S, Soutar AK. Familial hypercholesterolaemia in Portugal. *Atherosclerosis* 2008;**196**:633–42.

Briffaut D, Tounian P, Benlian P, Girardet J. Molecular-based diagnostic criteria of familial hypercholesterolemia in children with dominantly-inherited hypercholesterolemia. *J Pediatr Gastroenterol Nutr* 2000;**31**:S209.

Brusgaard K, Jordan P, Hansen H, Hansen AB, Horder M. *Molecular genetic analysis of* 1053 Danish individuals with clinical signs of familial hypercholesterolemia. *Clin Genet* 2006;**69**:277–83.

Bunn CF, Lintott CJ, Scott RS, George PM. Comparison of SSCP and DHPLC for the detection of LDLR mutations in a New Zealand cohort. *Hum Mutat* 2002;**19**:311.

Campagna F, Martino F, Bifolco M, Montali A, Martino E, Morrone F, *et al.* Detection of familial hypercholesterolemia in a cohort of children with hypercholesterolemia: results of a family and DNA-based screening. *Atherosclerosis* 2008;**196**:356–64.

Cefalu AB, Emmanuele G, Marino G, Fiore B, Caldarella R, Vivona N, *et al.* Effectiveness of screening for known mutations in Sicilian patients with 'probable' familial hypercholesterolemia. *Nutr Metab Cardiovasc Dis* 2001;**11**:394–400.

Charng MJ, Chiou KR, Chang HM, Cheng HM, Ye ZX, Lin SJ. Identification and characterization of novel low-density lipoprotein receptor mutations of familial hypercholesterolaemia patients in Taiwan. *Eur J Clin Invest* 2006;**36**:866–74.

Chaves FJ, Real JT, Garcia-Garcia AB, Civera M, Armengod ME, Ascaso JF, *et al.* Genetic diagnosis of familial hypercholesterolemia in a South European outbreed population: influence of low-density lipoprotein (LDL) receptor gene mutations on treatment response to simvastatin in total, LDL, and high-density lipoprotein cholesterol. *J Clin Endocrinol Metab* 2001;**86**:4926–32.

Chiou K-R, Charng M-J. Detection of mutations and large rearrangements of the low-density lipoprotein receptor gene in Taiwanese patients with familial hypercholesterolemia. *Am J Cardiol* 2010;**105**:1752–8.

Chmara M, Wasag B, Zuk M, Kubalska J, Wegrzyn A, Bednarska-Makaruk M, *et al.* Molecular characterization of Polish patients with familial hypercholesterolemia: novel and recurrent LDLR mutations. *J Appl Genet* 2010;**51**:95–106.

Cohen H, Harats D, Wael N, Anikster Y, Mazor-Aronovitch K, Pinhas-Hamiel O. LDL receptor mutation in a druze kindred – clinical, biochemical and genetic characteristics. *Atheroscler Suppl* 2009;**10**:e1222.

Damgaard D, Nissen PH, Jensen LG, Nielsen GG, Stenderup A, Larsen ML, *et al.* Detection of large deletions in the LDL receptor gene with quantitative PCR methods. *BMC Med Genet* 2005;**6**:15.

De Castro-Ors I, Palacios L, Pampn S, Plana N, Masana L, Stef M, *et al.* Functional analysis of LDLR promoter mutations associated with familial hypercholesterolemia. *Atheroscler Suppl* 2010;**11**:112–3.

Dedoussis GVZ, Skoumas J, Pitsavos C, Choumerianou DM, Genschel J, Schmidt H, *et al.* FH clinical phenotype in Greek patients with LDL-R defective vs. negative mutations. *Eur J Clin Invest* 2004;**34**:402–9.

Defesche JC. Is molecular genetic testing for familial hypercholesterolemia cost effective and clinically useful? *Atheroscler Suppl* 2006;**7**:19.

Diakou M, Miltiadous G, Xenophontos S, Cariolou M, Elisaf M. Mutational analysis in northwestern Greece patients with clinical diagnosis of familial hypercholesterolemia. *Atheroscler* 2009;**10**(Suppl.):e1224.

Diakou M, Miltiadous G, Xenophontos S, Cariolou M, Heta N, Korita I, *et al.* Characterization of low density lipoprotein receptor (LDLR) gene mutations in Albania. *Arch Med Sci* 2010;**6**:198–200.

Ejarque I, Real JT, Martinez-Hervas S, Chaves FJ, Blesa S, Garcia-Garcia AB, *et al.* Evaluation of clinical diagnosis criteria of familial ligand defective apoB 100 and lipoprotein phenotype comparison between LDL receptor gene mutations affecting ligand-binding domain and the R3500Q mutation of the apoB gene in patients from a South European population. *Transl Res* 2008;**151**:162–7.

El MM, Ait CK, Chater R, Vallve JC, Bennis F, Hafidi A, *et al.* Familial hypercholesterolemia in Morocco: first report of mutations in the LDL receptor gene. *J Hum Genet* 2003;**48**:199–203.

Emi M, Hirayama T, Tsuji M, Hata A. Novel mutations of the LDL receptor gene in familial hypercholesterolemia pedigrees in Hokkaido. In Kita T, Yokode M, editors. *Lipoprotein metabolism and atherogenesis*. Springer Verlag; 2000. pp. 48–50.

Fouchier SW, Defesche JC, Umans-Eckenhausen MAW, Kastelein JJP. The molecular basis of familial hypercholesterolemia in the Netherlands. *Hum Genet* 2001;**109**:602–15.

Fouchier SW, Kastelein JJP, Defesche JC. Update of the molecular basis of familial hypercholesterolemia in The Netherlands. *Hum Mutat* 2005;**26**:550–6.

Garcia-Garcia AB, Real JT, Puig O, Cebolla E, Marin-Garcia P, Martinez Ferrandis JI, *et al.* Molecular genetics of familial hypercholesterolemia in Spain: ten novel LDLR mutations and population analysis. *Hum Mutat* 2001;**18**:458–9.

Graham CA, McIlhatton BP, Kirk CW, Beattie ED, Lyttle K, Hart P, *et al.* Genetic screening protocol for familial hypercholesterolemia which includes splicing defects gives an improved mutation detection rate. *Atherosclerosis* 2005;**182**:331–40.

Guardamagna O, Restagno G, Rolfo E, Pederiva C, Martini S, Abello F, *et al.* The type of LDLR gene mutation predicts cardiovascular risk in children with familial hypercholesterolemia. *J Pediatr* 2009;**155**:199–204.

Hadfield SG, Horara S, Starr BJ, Yazdgerdi S, Bhatnagar D, Cramb R, *et al.* Are patients with familial hypercholesterolaemia well managed in lipid clinics? An audit of eleven clinics from the Department of Health Familial Hypercholesterolaemia Cascade Testing project. *Ann Clin Biochem* 2008;**45**:199–205.

Hadfield SG, Horara S, Starr BJ, Yazdgerdi S, Marks D, Bhatnagar D, *et al.* Family tracing to identify patients with familial hypercholesterolaemia: the second audit of the Department of Health Familial hypercholesterolaemia Cascade Testing project. *Ann Clin Biochem* 2009;**46**:24–32.

Heath KE, Humphries SE, Middleton-Price H, Boxer M. A molecular genetic service for diagnosing individuals with familial hypercholesterolaemia (FH) in the United Kingdom. *Eur J Hum Genet* 2001;**9**:244–52.

Higgins S, Stay C, Duxbury N, Smit C. Validation of Elucigene QST*R, a QF-PCR Assay. *J Med Genet* 2006;**43**:S102.

Huijgen R, Kindt I, Fouchier S, Defesche J, Hutten B, Kastelein J, *et al.* Non-functionality of three LDL-R and APOB gene mutations that were assumed to cause familial hypercholesterolemia. *Atheroscler Suppl* 2009;**10**:e1231.

Huijgen R, Versmissen J, Oosterveer DM, Kindt I, Sijbrands EJG, Kastelein JJP. Efficacy of 15 years of genetic cascade screening for familial hypercholesterolemia in the Netherlands in prevention of coronary artery disease. *Atheroscler Suppl* 2010;**11**:L6.

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Appendix 8

Characteristics of the included studies

Study details	Participants	Test characteristics	Outcomes reported	Comments
Alonso 2009[39] Study design: cross-sectional comparative Publication type: full text Other related reports: none Number of study centres: 11 Spanish regions Setting: NR Country: Spain Recruitment date: screening started in 2004 Patients recruited consecutively, Y/N: NR Source of funding: NR	Inclusion criteria: unrelated cases with clinical diagnosis of FH after the affiliation of the Dutch Lipid Clinic Network criteria with a score of ≥ 6 points Exclusion criteria: NR Clinical diagnosis of index cases: Dutch criteria Participants: all index cases FH diagnosis: definite FH or probable FH **Index cases** Enrolled, *n*: 808 Analysed, *n*: 808	**Test 1**: LIPOchip platform, which comprises: Stage 1 (index test): DNA array that can detect 191 different point mutations in *LDLR* and four different mutations in *APOB* (no *PCSK9* analysis) Stage 2 (part of CGA): adapted QMFSP for the analysis of large deletions or insertions Stage 3 (part of CGA): sequencing of *LDLR* gene using MegaBace 1000 apparatus **Stage 1**: Received test, *n*: 808 **Stage 2**: 389 **Stage 3**: 312 Reproducibility evaluation: Blind analysis of FH samples from Spain and the Netherlands was performed. Dutch FH samples (*LDLR* point mutations) analysed with DNA array = 53; Spanish FH samples (positive for large deletions and insertions) analysed with MLPA in Dutch laboratory = 43 (not all received CGA)	Diagnostic accuracy (sensitivity and specificity) of the DNA array Reproducibility Number diagnosed with positive test for each stage of test and total test Time taken to complete the LIPOchip platform and to obtain each test result	Sensitivity of the DNA array: determined by the number of mutations detected by sequencing *LDLR* in the samples in which the DNA array failed to detect mutations Specificity of the DNA array: 125 different DNA array-positive samples were randomly selected and sequenced automatically
Callaway 2010[40] Study design: cross-sectional comparative Publication type: presentation plus information from author Other related reports: none Number of study centres: 1 Setting: NR Country: UK Recruitment date: NR Patients recruited consecutively, Y/N: NR Source of funding: NR	Inclusion criteria: samples selected for validation were 10 normal control, 6 Elucigene FH20 positive control, 22 Elucigene FH20 negative control subjects Exclusion criteria: NR Clinical diagnosis of index cases: definite FH on referral card; or high cholesterol level (> 8 mmol/l) plus either (1) family history of high cholesterol or (2) family history of cardiovascular disease Participants: NR FH diagnosis: definite FH or probable FH **Patients** Enrolled, *n*: 22	**Test 1**: LIPOchip platform consisting of two stages: Stage 1 (index test): LIPOchip version 8 detects point mutations in the *LDLR*, *APOB* and *PCSK9* genes and copy number changes in the *LDLR* gene. Includes 251 mutations most prevalent in Spain, the Netherlands, Norway, Italy and the UK Stage 2 (component of CGA): sequencing of *LDLR* if no mutation was detected by LIPOchip **Test 2**: Elucigene FH20 (included *APOB* and *PCSK9*)/ dHPLC/ sequencing of *LDLR* gene/MLPA **Test 1**: Received test, *n*: 22 **Test 2**: 22	Diagnostic accuracy (sensitivity and specificity) of LIPOchip	

Study details	Participants	Test characteristics	Outcomes reported	Comments
Civeira 2008[44] Study design: cross-sectional comparative, retrospective Publication type: full text Other related reports: Tejedor 2005,[43] Tejedor 2006[56] (for LIPOchip test) Number of study centres: 3 Setting: lipid clinics Country: Spain Study dates: May 2004–November 2007 Patients recruited consecutively, Y/N: Y Source of funding: NR	Inclusion criteria: patients aged ≥ 14 years, evaluated at three large clinics for clinical diagnosis and underwent the FH genetic diagnostic procedure using LIPOchip. Patients were retrospectively categorised into Simon Broome criteria, Dutch criteria and MedPed criteria Exclusion criteria: NR Participants: adults and adolescents, index cases Clinical diagnosis: MedPed criteria for initial diagnosis (by attending physicians), which includes very high TC or LDL-C levels, with or without tendon xanthomata, with or without familial or personal histories of premature CAD FH diagnosis: definite FH or possible FH **Index cases** Enrolled, *n* 825 Analysed, *n* 825 Age, years Sex, M/F 438/387 CAD, *n* 17 Personal history of CAD, *n* 105 Xanthomata, *n* 195	**Test 1**: LIPOchip platform (203 mutations in *LDLR* and 4 mutations in *APOB*) as follows: (1) DNA array (2) Quantitative fluorescence-based multiplex polymerase chain reaction for analysis of large gene rearrangements in samples with negative results from DNA array (3) sequencing of the promoter, all exons and the exon/intron boundaries of the *LDLR* gene for samples with negative results from above test Test was carried out in Spain **Test 2**: lipid measurements were determined using standard enzymatic methods. LDL-C concentration was estimated from a fasting blood sample using the Friedwald equation when serum triglyceride levels were < 400 mg/dl **Test 1** / **Test 2** Enrolled, *n* 825 / 825 Analysed, *n* 825 / 825	Diagnostic accuracy of Simon Broome, MedPed and Dutch criteria Detection rate of FH by LIPOchip platform	

Study details	Participants	Test characteristics	Outcomes reported	Comments
Damgaard 2005[45] Study design: cross-sectional comparative, retrospective Publication type: full text Other related reports: Starr 2008[49] Number of study centres: 1 Setting: lipid clinics Country: Denmark Study dates: January 1995–December 2003 Patients recruited consecutively, Y/N: Y Sources of funding: Danish Heart Foundation and Institute of Experimental Clinical Research at the University of Aarhus	Inclusion criteria: patient referred for FH to the lipid clinic. Patient with any two of the following criteria: LDL-C cut-offs >6 mmol/l, TC >8 mmol/l, tendon xanthomata and history of CAD before the age of 60 years in the patient and/or in a first-degree relative and/or hypercholesterolaemia in a first-degree relative Exclusion criteria: secondary hypercholesterolaemia, renal failure, nephritic syndrome, liver disease, hypothyroidism and diabetes Participants: adults; index cases and relatives of index cases in whom a mutation was identified Clinical diagnosis: index patients were categorised retrospectively based on lipid measurements and clinical examination before genetic analysis into Simon Broome, Dutch and MedPed criteria FH diagnosis: definite FH, possible FH or probable FH	**Test 1:** (comparator test): LDL-C concentration estimated from a fasting blood sample using Friedwald equation LDL-C as part of Simon Broome DNA sequence analysis Genes tested: *LDLR* (including deletions) and *APOB* **Test 2:** (reference standard): genetic test performed in following stages: (1) routine screening for three common mutations in the *LDLR* gene in Danish population (all) (2) SSCP for those with negative mutation (3) sequencing for those with negative mutation (69 patients) (4) analysis of *APOB* gene (all) (5) MLPA for those with negative mutation **Test 3**: targeted sequencing of relatives for the mutation found in the index patient of the family: Tests were performed in Denmark	Diagnostic accuracy of LDL-C as part of Simon Broome and Dutch criteria and LDL-C age- and gender-specific MedPed criteria to diagnose FH	

	FH	Not FH
Enrolled, **n**		
Index cases	408	
Relatives	385	
Analysed, **n**		
Index cases[a]	133	273
Relatives	203	180
Age, years, mean	*LDLR*=42.6 *APOB*=45.5	52
Sex, M, *n*	140	266
CAD, *n*	34	61
Tendon xanthomata, *n*	41	25

a Two double heterozygous patients excluded

	Test 1	Test 2	Test 3
Analysed, *n*			
Index cases	408	408	
Relatives			385

Study details	Participants	Test characteristics	Outcomes reported	Comments
Hooper 2009[36] Study design: cross-sectional Publication type: conference abstract Other related reports: Poke 2009[97] Number of study centres: NR Setting: NR Country: Australia Recruitment date: NR Patients recruited consecutively, Y/N: NR Source of funding: NR	Inclusion criteria: patients with a diagnosis of definite FH based on Dutch Lipid Clinic criteria enrolled in the FH Western Australia (FHWA) pilot programme Exclusion criteria: NR Clinical diagnosis: Dutch criteria FH diagnosis: all definite FH **Index cases** Enrolled, *n*: 63 Analysed, *n*: 63	**Test 1**: genetic test consisting of three stages: Stage 1 (index test): Elucigene FH20 for the detection of 20 common mutations Stage 2 (part of CGA): MLPA for the detection of deletions/duplications Stage 3 (part of CGA): Exon-by-exon sequencing of the *LDLR* gene **Stage 1 / Stage 2 / Stage 3** Received test, *n*: 63 / 49 / 43 Not all received sequencing and MLPA	Number of patients with mutation detected by each stage of test and combination of tests	
Lee 2010[48] Study design: cross-sectional, retrospective Publication type: abstract (additional information from author) Other related reports: none Number of study centres: NR Setting: NR Country: UK Study dates: 2005–10 Patients recruited consecutively, Y/N: NR Source of funding: NR	Inclusion criteria: index patients with a definite diagnosis of homozygous FH based on Simon Broome criteria and genetic test, recruited from an ongoing national cascade testing project, and their relatives Exclusion criteria: NR Participants: relatives of genotyped FH index cases Clinical diagnosis: Simon Broome and then Dutch scoring FH diagnosis: definite FH or possible FH **Index cases / Relatives** Enrolled, *n*: 30 / 90 Analysed, *n*: 30 / 90 Homozygous FH, *n*: 30 / NR	**Test 1**: genetic test as follows in three separate laboratories: Laboratory 1 (biochemistry, Wales): Elucigene FH20/ dHPLC/MLPA Laboratory 2 (Progenika): LIPOchip/sequencing Laboratory 3 (Belfast): iPLEX (50 mutations)/sequencing/ MLPA Genes tested: *LDLR*, *APOB*, *PCSK9* **Test 2**: Sex- and age-adjusted LDL-C values based on Dutch scoring criteria to determine eligibility for genotyping of relatives **Test 1 / Test 2** Analysed, *n*: 90 / 90	Detection rate of Elucigene FH20 of index cases as of 2010 (34/104 index patients = 32%) Diagnostic accuracy of test 2 on relatives	

<table>
<tr><th>Study details</th><th>Participants</th><th>Test characteristics</th><th>Outcomes reported</th><th>Comments</th></tr>
<tr>
<td>Mabuchi 2005[46]
Study design: case–control
Publication type: full text
Other reports this study may link with: Yu 2002[51]
Number of study centres: NR
Setting: NR
Country: Japan
Recruitment date: NR
Patients recruited consecutively, Y/N: NR
Source of funding: NR</td>
<td>Inclusion criteria: patients with definite FH (LDLR gene mutation) and unaffected first- and second-degree relatives (without LDLR gene mutation)
Exclusion criteria: those who had a disease affecting serum lipid concentrations
Participants: adults; index cases and first- and second-degree unaffected relatives
Clinical diagnosis: NR
FH diagnosis: NR
<table>
<tr><th></th><th>FH</th><th>No FH</th></tr>
<tr><td>Enrolled, n</td><td>181</td><td>100</td></tr>
<tr><td>Analysed, n</td><td>181</td><td>10</td></tr>
<tr><td>Age, years, mean (SD)</td><td>41.9 (16.7)</td><td>35.1 (17.7)</td></tr>
<tr><td>Sex, M/F, n</td><td>91/90</td><td>51/49</td></tr>
<tr><td>Homozygous FH, n</td><td>0</td><td>N/A</td></tr>
</table>
N/A, not applicable.</td>
<td>Test 1: genetic test as follows:
(1) PCR/DGGE/direct sequencing of LDLR gene
(2) Southern blot analysis to detect large rearrangements
Test 2: LDL-C estimated from a fasting blood sample using Friedwald equation. LDL-C cut-offs > 4.0 mmol/l and TC > 5.8 mmol/l established through bimodal distributions of TC and LDL-C
<table>
<tr><th></th><th>Test 1</th><th>Test 2</th></tr>
<tr><td>Received test, n</td><td>281</td><td>281</td></tr>
<tr><td>FH, n</td><td>181</td><td></td></tr>
<tr><td>No FH, n</td><td>100</td><td></td></tr>
</table></td>
<td>Diagnostic test accuracy of LDL-C concentration</td>
<td>Studies with genetically identified patients in whom clinical cut-offs were retrospectively applied</td>
</tr>
</table>

Study details	Participants	Test characteristics	Outcomes reported	Comments
Palacios 2010[41,52] Study design: cross-sectional, comparative Recruitment data: NR Patients recruited consecutively, Y/N: NR Publication type: abstract Other related reports: Stef 2010[52] (presentation from Progenika Biopharma), plus some additional data from Progenika Biopharma Number of study centres: 2 Setting: NR Country: UK Recruitment date: Patients recruited consecutively, Y/N: Source of funding: Progenika Biopharma Stef 2010:[52] samples from two centres were included (Newcastle and Wales); however, the Welsh samples do not have information on clinical diagnosis and also do not have previous genetic diagnosis (according to response to queries from the manufacturer), hence study was not included for the review purpose	Inclusion criteria: DNA samples from patients with clinical diagnosis based on Simon Broome criteria and previously tested with genetic test (ARMS + SSCP/dHPLC/direct sequencing + MLPA) Exclusion criteria: NR Clinical diagnosis: Simon Broome criteria FH diagnosis: NR **Index cases** Enrolled, *n*: 126 Analysed, *n*: 120	**Test 1**: LIPOchip platform consisting of two stages: Stage 1 (index test): LIPOchip version 8 detects point mutations in the *LDLR*, *APOB* and *PCSK9* genes and copy number changes in the *LDLR* gene. Includes 251 mutations most prevalent in Spain, the Netherlands, Norway, Italy and the UK Stage 2 (component of CGA): sequencing of *LDLR* if no mutation was detected by LIPOchip **Test 2**: genetic screening in three stages (CGA): Stage 1: Elucigene (*APOB*, *PCSK9* included) Stage 2: SSCP/dHPLC/direct sequencing of all exons if no mutation was detected Stage 3: MLPA if no mutation was detected **Test 1** **Stage 1**: Enrolled, *n*: 126; Received test, *n*: 120 **Stage 2**: 89 **Test 2**: 126 mutation positive	Patients with mutation detected by each test Diagnostic accuracy Time taken to obtain positive results with LIPOchip platform (test was performed by Progenika in Spain)	LIPOchip UK version 10 was developed by analysing 1000 patients from several cohorts. The chip contains the most frequent mutations found in the UK as well as having the ability to detect copy number changes in the *LDLR* gene

Study details	Participants	Test characteristics	Outcomes reported	Comments
Starr 2008[49] Study design: cross-sectional comparative, retrospective Publication type: full text Other reports this paper may link with: Leren 2004[53] (Norway), Umans-Eckenhausen 2001[19] (the Netherlands), Damgaard 2005[45] (Denmark); samples come from these studies. Number of study centres: 3 Setting: lipid clinics Country: UK Recruitment date: NR Patients recruited consecutively, Y/N: NR Sources of funding: Department of Health, British Heart Foundation. One author supported by the Department of Trade and Industry for the IDEAS Genetics Knowledge Park	Inclusion criteria: a data set of a cohort of relatives of known mutation status (previously genetically tested) from a European country (the Netherlands, Norway, Denmark) Exclusion criteria: those on lipid-lowering therapy, non-fasting samples and those with triglyceride levels of >2 mmol/l Participants: first-degree relatives with known mutational status of FH index cases in whom a mutation had been found Clinical diagnosis: based on Dutch criteria (the Netherlands); a combination of lipid levels, clinical characteristics and family history (Norway and Denmark) FH diagnosis: definite FH or possible FH	**Test 1**: CGA (DGGE/direct sequencing/PCR or screening of three common mutations in Danish population/SSCP/sequencing/MLPA or sequencing/MLPA) **Test 2**: lipid tests The Netherlands: blood sample measured using cholesterol analysis equipment (calibrated). Subjects refrained from eating for 2 hours before test Norway: cholesterol was measured using Roche modular Pinstrument (method standardised). Results from non-fasting samples excluded Denmark: validated with reference standard LDL-C was calculated according to the Friedwald formula Age- and gender-specific LDL-C cut-offs according to NICE guideline used **Test 3**: MedPed age-specific LDL-C cut-offs for relatives For all tests:	Diagnostic accuracy of age- and gender-specific LDL-C vs genetic tests	

The Netherlands	**Mut+**	**Mut–**
Enrolled, *n*	825	2469
Analysed, *n*	825	2469
Age, years, mean (SD)	30.7 (18.1)	42.8 (19.3)
Sex, M %	50	44
LDL-C, mmol/l, mean (SD)	4.36 (1.39)	3.02 (0.94)
TC, mmol/l, mean (SD)	6.23 (1.43)	4.99 (1.05)
Denmark	**Mut+**	**Mut–**
Analysed, *n*	160	161
Age, years, mean (SD)	35.5 (15.0)	41.2 (16.9)
Sex, M %	44	43
LDL-C, mmol/l, mean (SD)	5.72 (1.86)	3.56 (1.14)
TC, mmol/l, mean (SD)	7.74 (1.88)	5.64 (1.28)

Received test, *n*	**Mut+**	**Mut–**
The Netherlands	825	2469
0–14 years	183	243
15–24 years	187	276
25–34 years	138	293
35–44 years	136	471
45–54 years	92	449
55+ years	89	737

Study details	Participants	Test characteristics	Outcomes reported	Comments

Norway	Mut+	Mut-
Analysed, *n*	374	742
Age, years, mean (SD)	27.3 (17.2)	37.0 (18.5)
Sex, M/F %	46	46
LDL-C, mmol/l, mean (SD)	5.71 (1.69)	3.4 (1.03)
TC, mmol/l, mean (SD)	7.74 (1.88)	5.64 (1.28)

Received test, *n*	Mut+	Mut–
Denmark[a]	160	161
0–14 years		
15–24 years	42	23
25–34 years	34	36
35–44 years	39	27
45–54 years	18	29
55+ years	22	50
Norway	374	742
0–14 years	106	107
15–24 years	82	103
25–34 years	69	124
35–44 years	51	145
45–54 years	39	120
55+ years	27	143

a Please note that all the figures presented in this table were sourced from Starr and colleagues,[49] where an error was observed in the total number reported for the Denmark group (the age subgroups do not add to the total reported). Authors were unable to get the correct values from the original source

Study details	Participants	Test characteristics	Outcomes reported	Comments
Stef 2009[42] Study design: cross-sectional Publication type: conference abstract Other reports: none Number of study centres: NR Setting: NR Country: Spain Recruitment date: NR Patients recruited consecutively, Y/N: NR Source of funding: Progenika Biopharma	Inclusion criteria: NR Exclusion criteria: NR Clinical diagnosis: Dutch–MedPed criteria FH diagnosis: NR **Index cases** Enrolled, *n*: 2462 Analysed, *n*: 2462	**Test 1**: LIPOchip platform consisting of two stages: Stage 1 (index test): LIPOchip Spanish version containing 247 most frequent Spanish mutations (238 *LDLR*, three *APOB* and six *PCSK9*). LIPOchip detects point mutations in the *LDLR*, *APOB* and *PCSK9* genes and copy number changes in the *LDLR* gene Stage 2 (part of CGA): sequencing of the entire *LDLR* gene for those negative on LIPOchip Number receiving test for each stage of tests not reported Not all received sequencing	Percentage of patients with mutation detected by LIPOchip and combination of tests	
Tejedor 2005[43] Study design: cross-sectional comparative Publication type: full text Other reports: Oliva 2009,[57] Tejedor 2006[56] Number of study centres: 70 Setting: lipid clinics Country: Spain Recruitment date: NR Patients recruited consecutively, Y/N: NR Source of funding: NR	Inclusion criteria: genotyped FH identified by SSCP/sequencing/restricted polymorphism and non-genotyped FH based on Dutch–MedPed criteria from Spanish national register Exclusion criteria: NR Clinical diagnosis: Dutch–MedPed criteria FH diagnosis: definite FH based on clinical score of ≥ 8 points and probable or possible FH with score of 4–8 **Phenotyped (*n* = 407)** **DFH** / **PFH** Enrolled, *n*: 252 / 155 Adults Children Received test, *n*: 252 / 155 Analysed, *n*: 252 / 155 Age, years, mean (SD): 47.6 (14.2) / 46.0 (18.1) Sex, M/F, *n*: 126/126 / 62/93 PCVD: 18.7% / 6.8% Tendon xanthomata: 33.1% / 23.7%	**Test 1**: LIPOchip, earliest Spanish version Stage 1 (index test): DNA array including 118 mutations (117 *LDLR* and 1 *APOB*) as identified from SSCP/sequencing/restriction polymorphism analysis (more than half of these mutations have been reported in Western Europe (Holland, France, Germany, Italy, Greece and the UK) and the USA Stage 2 (part of CGA): sequencing of *LDLR* gene for mutation-negative samples on DNA array **Stage 1** / **Stage 2** Patients analysed, *n*: 407 / 123 (DFH) Not all received sequencing Genotyped patients (1180) were used to test specificity and sensitivity of DNA array	Number of patients with mutation detected by each stage of test PCVD-free survival time depending on the type of mutation based on the Kaplan–Meier curves with age limits of 55 years in men and 65 years in women for DNA array Sensitivity and specificity of DNA array to detect mutations that are included in the DNA array (tests were performed in Spain)	

Study details	Participants	Test characteristics	Outcomes reported	Comments
Taylor 2010[37,54] Study design: cross-sectional Publication type: full text Other related reports: Tabrah 2005,[55] Taylor 2009,[28] Taylor 2007[54] Number of study centres: 6 (5 for cascade testing) Setting: lipid clinics Country: UK Study date: 3 years Patients recruited consecutively, Y/N: Y Sources of funding: Departments of Health and Trade Industry for the IDEAS Genetics Knowledge Park and British Heart Foundation	Inclusion criteria: sample of unrelated patients attending one of six clinics in the UK and all received DNA analysis Exclusion criteria: NR Participants: adults; index cases and first-degree relatives Clinical diagnosis: Simon Broome criteria FH diagnosis: definite FH, possible FH or unclassified FH (unclassifiable because of the information provided, usually missing untreated cholesterol data)	Genes tested: *LDLR*, *APOB*, *PCSK9* **Test 1**: genetic tests performed in following sequence: Stage 1 (index test): Elucigene FH20 Stage 2 (part of reference standard): DNA sequence analysis of promoter, all exons, the exon/intron boundaries, 3′ untranslated region of the *LDLR* gene using SSCP/dHPLC/direct sequencing for those with negative mutation on Elucigene FH20 Stage 3 (part of reference standard): MLPA for the detection of deletions/duplications for those with negative mutation on sequencing **Test 2**: targeted sequencing of relatives of index cases with identified mutation Tests performed in the UK	Detection rate of FH Detection rate of FH by ethnicity Detection rate of cascade testing Mutation detection rate of Elucigene FH20	Elucigene FH013 B1 kit (11 *LDLR*+1 *APOB*+1 *PCSK9*) was used for initial testing. Detection rate data from these tests were combined as if samples were tested using FH20

	DFH	PFH	UFH	Total
Enrolled, **n**				
Index cases	190	394	51	635
Relatives	138	146	12	296
Analysed, **n**				
Index cases	190	394	51	635
Relatives	138	146	12	296
Ethnicity, **n**				
White British[a]				397
Europe				37
Middle East				11
Indian Asian				31
Afro-Caribbean				8
Far East[b]				6
NR				145

a Includes British Jewish
b Includes Chinese, Thai, Philippino

	Test 1			
	Stage 1	Stage 2	Stage 3	Test 2
Analysed, **n**				
DFH	190	138	87	138
PFH	394	349	287	146
UFH	51	46	40	12
Total	635	533	414	296

<table>
<tr><th>Study details</th><th>Participants</th><th>Test characteristics</th><th>Outcomes reported</th><th>Comments</th></tr>
<tr>
<td>Wiegman 2003[50]
Study design: cross-sectional comparative
Publication type: full text
Other reports: Fouchier 2001,[58] Koeijvoets 2005[98]
Number of study centres: NR
Setting: lipid clinics
Country: the Netherlands
Study dates: July 1989–July 2001
Patients recruited consecutively, Y/N: NR
Source of funding: NR</td>
<td>Inclusion criteria: children from parents with a diagnosis of heterozygous FH referred to a lipid clinic
Exclusion criteria: NR
Participants: children of FH parents
Clinical diagnosis: parents' diagnosis of heterozygous FH was based on a documented LDLR mutation or plasma LDL-C levels > 95th percentile for age and gender in a family with a history of PCVD in conjunction with tendon xanthomata. Children's diagnosis was based on age- and gender-specific LDL-C levels > 3.50 mmol/l cut-offs for those whose genetic test not yet calculated
FH diagnosis: definite FH or possible FH
<table>
<tr><th></th><th>FH genetic diagnosis</th><th>FH not yet confirmed with genetic test</th><th>Total</th></tr>
<tr><td>Enrolled, n</td><td></td><td></td><td></td></tr>
<tr><td>Index cases</td><td>591</td><td></td><td></td></tr>
<tr><td>Children</td><td>806</td><td>228</td><td>1034</td></tr>
<tr><td>Analysed</td><td>806</td><td>228</td><td>1034</td></tr>
</table>
</td>
<td>Test 1 (reference standard): genetic testing includes DNA sequence analysis of the coding region of the LDLR gene
Test 2: clinical test that includes age- and gender-specific LDL-C levels > 3.50 mmol/l cut-offs
Plasma TC, high-density lipoprotein cholesterol and triglycerides measured using commercial kits. LDL-C calculated by Friedwald equation
<table>
<tr><th></th><th>Test 1</th><th>Test 2</th></tr>
<tr><td>Enrolled, n</td><td>1034</td><td>282</td></tr>
<tr><td>Analysed, n</td><td>806</td><td>228</td></tr>
</table>
</td>
<td>FH detection rates of children by both tests
Test accuracy data</td>
<td></td>
</tr>
</table>

Study details	Participants	Test characteristics	Outcomes reported	Comments
Widhalm 2007[47] Study design: cross-sectional comparative Publication type: full text Other related reports: none Number of study centres: NR Setting: lipid clinics Country: Austria Recruitment date:1997 Patients recruited consecutively, Y/N: NR Source of funding: NR	Inclusion criteria: children and adolescents (<18 years) and their families with definite FH or possible FH Exclusion criteria: NR Participants: index cases <18 years; relatives adult (all presented as index cases in the study) Clinical diagnosis: MedPed criteria FH diagnosis: definite FH (family had at least one member with confirmed FH) and possible FH (whose family had no member with proven FH)	**Test 1**: clinical test Index cases = LDL-C levels > 5.1 mmol/l, relatives = LDL-C levels > 4 mmol/l, age specific (all treated as index cases) Lipid measurements using commercial kit. LDL-C concentration measurement estimated from fasting blood sample using the Friedwald equation. LDL-C measured twice Test was performed in the Lipoprotein Research Laboratory, Vienna **Test 2**: genetic test as follows: (1) PCR/DGGE/sequencing of the *LDLR* gene (2) *APOB* analysis Test was performed in the Institute of Medical Biochemistry, Austria	FH detection rates by clinical and genetic tests	

Index cases

***Enrolled,* n**	
Total	263
Adults	147
Children	116
Sex, M/F	
Adults	83/64
Children	59/57
Current treatment for high cholesterol	14 on statins; DFH received dietary treatment
LDL-C, mg/dl, mean (SD)	
Adults, M/F	203 (70)/187 (52)
Children, M/F	170(60)/166 (68)
TC, mmol/l, mean (SD)	
Adults, M/F	292 (100)/268 (59)
Children, M/F	250 (74)/240 (67)

	Test 1	Test 2
Received test, *n*	119[a]	263
Adults, *n*	62	147
Children, *n*	57	116
Analysed, *n*	119	263

a Genetically confirmed FH

<table>
<tr><th>Study details</th><th>Participants</th><th>Test characteristics</th><th>Outcomes reported</th><th>Comments</th></tr>
<tr>
<td>Yarram 2010[38]
Study design: cross-sectional
Publication type: presentation
Other related reports: none
Number of study centres: 1
Setting: lipid clinics
Country: UK
Study date: NR
Patients recruited consecutively, Y/N: NR
Source of funding: NR</td>
<td>Inclusion criteria: NR
Exclusion criteria; NR
Participants: index cases and relatives
Clinical diagnosis: Simon Broome criteria with patients diagnosed as definite FH, possible FH, unclassified FH and not meeting criteria
<table>
<tr><th></th><th>DFH</th><th>PFH</th><th>UFH</th><th>No FH</th></tr>
<tr><td>Enrolled, n</td><td>131</td><td></td><td></td><td></td></tr>
<tr><td>Index cases, n</td><td>15</td><td>53</td><td>17</td><td>19</td></tr>
<tr><td>Relatives, n</td><td>27</td><td></td><td></td><td></td></tr>
</table>
</td>
<td>Test 1: genetic tests performed in following sequence:
Stage 1 (index test): Elucigene FH20
Stage 2 (part of reference standard): DNA sequence analysis of promoter and all exons of the LDLR gene using sequencing for those with negative mutation on Elucigene FH20
Those with positive mutation on Elucigene FH20 were confirmed with sequencing
Stage 3 (part of reference standard): MLPA for the detection of deletions/duplications for those with negative mutation on sequencing
Test 2: cascade test
<table>
<tr><th></th><th>Test 1</th><th>Test 2</th></tr>
<tr><td>Enrolled, n</td><td>104</td><td>27</td></tr>
</table>
</td>
<td>Sensitivity of Elucigene FH20
Sensitivity of LIPOchip (data not included in the report as were not cleared; author was contacted but no response so far)
Number testing positive
Proportion identified from cascade testing</td>
<td></td>
</tr>
</table>

ARMS, amplification-refractory mutation system; CAD, coronary artery disease; DFH, definite FH; N/A, not applicable. NR, not reported; PFH, possible FH; UFH, unclassified FH.

Appendix 9

Quality assessment results for the individual studies (full text)

	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8[a]	Q9	Q10	Q11[a]	Q12	Q13[a]
Taylor 2010[37]	+	+	–	–	+	+	?	N/A	–	–	N/A	+	N/A
Alonso 2009[39]	+	+	–	–	+	+	?	N/A	–	–	N/A	–	N/A
Tejedor 2005[43]	+	–	–	–	+	?	?	N/A	–	–	N/A	–	N/A
Civeira 2008[44]	+	+	+	–	+	+	?	+	–	–	+	+	+
Damgaard 2005[45]	+	+	+	+	+	?	?	+	+	–	+	+	+
Mabuchi 2005[46]	?	–	+	+	+	?	?	+	–	–	–	+	–
[b]Starr 2008[49]	+	+	+	+	+	–	+	+	–	–	–	+	–
Widhalm 2007[47]	+	–	+	+	+	+	?	+	–	–	+	+	+
Wiegman 2003[50]	+	–	+	+	+	?	?	+	–	–	–	+	–

+ ,yes; –, no; ?, unclear; N/A, not applicable.

a Questions 8, 11 and 13 were considered to be not applicable to studies reporting Elucigene FH20 or LIPOchip because the Elucigene and LIPOchip test results do not require subjective interpretation (Q8), the tests either detect a mutation or do not detect a mutation, there are no cut-off levels (Q11), and because a result is either positive or negative there is no need to provide a definition of a positive result (Q13).

b Of the three cohorts included in the study, two had the complete reference standard (Denmark, Norway) but one did not receive the MLPA test. With consensus this was judged as 'yes' by two reviewers.

The questions were: Q1, Spectrum representative?; Q2, Reference standard correctly classifies condition?; Q3, Partial verification bias avoided?; Q4, Differential verification bias avoided?; Q5, Incorporation bias avoided?; Q6, Test review bias avoided?; Q7, Diagnostic review bias avoided?; Q8, Clinical review bias avoided?; Q9, Uninterpretable results reported?; Q10, Withdrawals explained?; Q11, Cut-offs established before study started?; Q12, Index test technology unchanged since study?; Q13, Clear definition of 'positive' result?.

Appendix 10

Individual study results for Elucigene FH20/LIPOchip

TABLE 34 Individual study results for Elucigene FH20/LIPOchip at patient-level analysis

Study	Diagnosis	Criteria	Genes	Tests	Methods	Enrolled	Tested	Positive	Negative	TP	FP	FN	TN	Sensitivity	Specificity
Hooper 2009[36]	DFH	Dutch	*LDLR*/*APOB*/*PCSK9*	Reference standard (1 + 2 + 3)	Elucigene FH20 + MLPA for test-negative with Elucigene FH20 + sequencing for test-negative with MLPA		63	49	14						
	DFH		*LDLR*/*APOB*/*PCSK9*	1	Elucigene FH20		63	14	49	14		35	14	0.285714	NC
	DFH		*LDLR*	2	MLPA for test-negative with Elucigene FH20		49	6	43						
	DFH		*LDLR*	3	Sequencing for test-negative with MLPA		43	29	14						
Taylor 2007[54]	DFH	Simon Broome	*LDLR*/*APOB*/*PCSK9*	Reference standard (1 + 2)	Elucigene FH13 + SSCP/dHPLC	400	400	54		54		87	259		NC
	PFH		*LDLR*/*APOB*/*PCSK9*	Reference standard (1 + 2)	As above	400	400	87		87		54	259		NC
	Total		*LDLR*/*APOB*/*PCSK9*	Reference standard (1 + 2)	As above	400	400	141	259						
	DFH		*LDLR*/*APOB*/*PCSK9*	1	Elucigene FH13	400	400	28		28		113	259	0.518518	NC
	PFH		*LDLR*/*APOB*/*PCSK9*	1	As above	400	400	26		26		115	259	0.298850	NC
	Total		*LDLR*/*APOB*/*PCSK9*	1	As above	400	400	54	346	54		87		0.382979	
	Total		*LDLR*	2	SSCP/dHPLC	400	400	87	313	87		54	259	0.617021	NC

Study	Diagnosis	Criteria	Genes	Tests	Methods	Enrolled	Tested	Positive	Negative	TP	FP	FN	TN	Sensitivity	Specificity
Taylor 2010[37]	DFH	Simon Broome	*LDLR*/*APOB*/*PCSK9*	Reference standard (1 + 2 + 3)	Elucigene FH20 + SSCP/dHPLC/sequencing for test-negative with Elucigene FH20 + MLPA for test-negative with sequencing		190	107	83						
	PFH		*LDLR*/*APOB*/*PCSK9*	Reference standard (1 + 2 + 3)	As above		394	112	282						
	UFH		*LDLR*/*APOB*/*PCSK9*	Reference standard (1 + 2 + 3)	As above		51	13	38						
	Total		*LDLR*/*APOB*/*PCSK9*	Reference standard (1 + 2 + 3)	As above		635	232	403						
	DFH		*LDLR*/*APOB*/*PCSK9*	1	Elucigene FH20		190	52	138	52		55	83	0.485981	NC
	PFH		*LDLR*/*APOB*/*PCSK9*	1	As above		394	45	349	45		67	282	0.401786	NC
	UFH		*LDLR*/*APOB*/*PCSK9*	1	As above		51	5	46	5		8	38	0.384615	NC
	Total		*LDLR*/*APOB*/*PCSK9*	1	As above		635	102	533	102		130	403	0.439655	NC
	DFH		*LDLR*	2	SSCP/dHPLC/sequencing for test-negative with Elucigene FH20		138	51	87						
	PFH		*LDLR*	2	As above		349	62	287						
	UFH		*LDLR*	2	As above		46	6	40						
	Total		*LDLR*	2	As above		533	119	414						
	DFH		*LDLR*	3	MLPA for test-negative with sequencing		87	4	83						
	PFH		*LDLR*	3	As above		287	5	282						
	UFH		*LDLR*	3	As above		40	2	38						
	Total		*LDLR*	3	As above		414	11	403						

continued

TABLE 34 Individual study results for Elucigene FH20/LIPOchip at patient-level analysis (*continued*)

Study	Diagnosis	Criteria	Genes	Tests	Methods	Enrolled	Tested	Positive	Negative	TP	FP	FN	TN	Sensitivity	Specificity
Palacios 2010[41]	Total	Simon Broome	*LDLR*/*APOB*/*PCSK9*	Reference standard (1 + 2)	LIPOchip version 8 + sequencing for test negative with chip	126	120	65	55						
Newcastle samples	Total		*LDLR*/*APOB*/*PCSK9*	1	LIPOchip version 8 (UK version)	126	120	37	83	37	0	28	55	0.569231	NC
				2	Sequencing for test-negative with chip		83	28	55						
	Total		*LDLR*/*APOB*/*PCSK9*	3	Elucigene FH20 + SSCP/dHPLC/direct sequencing + MLPA	126	126	62	64	62	0	3	61	0.953846	NC
	Total		*LDLR*/*APOB*/*PCSK9*	4	LIPOchip version 10 (UK)	126		51		51	0	14	55	0.784615	NC
Stef 2009[42]	Total	Dutch–MedPed	*LDLR*/*APOB*/*PCSK9*	Reference standard	LIPOchip platform (LIPOchip + sequencing for test-negative with chip)		2462	1206	1265						
	Total		*LDLR*/*APOB*/*PCSK9*	1	LIPOchip Spanish version		2462	1140	1322	1140	0	66	1265	0.945274	NC
Alonso 2009[39]	DFH/probable	Dutch	*LDLR*/*APOB*	Reference standard (1+2+3)	LIPOchip platform (DNA array + QMFSP + sequencing) Spanish version	808	808	537	271						
	Total		*LDLR*/*APOB*	1	DNA array for 195 mutations		808	419	389	419	0	118	271	0.780261	NC
	Total		Re-arrangements in *LDLR*	2	QMFSP for test-negative with DNA array		389	77	312						
	Total		*LDLR*	3	Sequencing for test-negative with QMFSP		312	41	271						

Study	Diagnosis	Criteria	Genes	Tests	Methods	Enrolled	Tested	Positive	Negative	TP	FP	FN	TN	Sensitivity	Specificity
Tejedor 2005[43]	DFH/PFH	Dutch–MedPed	*LDLR*/*APOB*	Reference standard	LIPOchip (DNA array only + sequencing) Spanish version		NR								
	DFH		*LDLR*/*APOB*	1	DNA array for 118 mutations	252	252	129							
	PFH		*LDLR*/*APOB*	1	As above	155	155	58							
	Total		*LDLR*/*APOB*	1	As above	407	407	187	220					NC	NC
	DFH		*LDLR*/*APOB*	2	Sequencing for test-negative with DNA array	123	123	43	80						
Manufacturer data for version 10 LIPOchip	NR	NR	*LDLR*/*APOB*/*PCSK9*		LIPOchip platform (LIPOchip + sequencing) + MLPA		NR								
					LIPOchip version 10	138 samples	138	198	130					NC	NC

DFH, definite FH; FN, false-negative; FP, false-positive; NC, not calculable; NR, not reported; PFH, possible FH; TN, true-negative; TP, true-positive; UFH, unclassified FH.

TABLE 35a Mutational-level analysis: analytical accuracy of LIPOchip as reported in the paper

Study	Criteria	Total, *n*	Mutation samples	TP	FP	TN	FN	Sensitivity (%)	Specificity (%)
Alonso 2009[39]	Dutch criteria – DFH or probable FH	808 phenotyped cases	178 real positive calls; 442 real negative calls	177	1	441	1	99.8	99.5
Tejedor 2005[43]	Dutch–MedPed criteria	1180 genotyped; 407 blind phenotyped samples	118 of the *LDLR* mutations tested with 1180 previously sequenced DNA samples and 10 control DNA samples	NR	NR	NR	NR	99.9	99.7
Manufacturer data for version 10 LIPOchip			Against the mutation already present in LIPOchip version 9	NR	NR	NR	NR	100	100

DFH, definite FH; FN, false-negative; FP, false-positive; NR, not reported; TN, true-negative; TP, true-positive.

TABLE 35b Mutational-level analysis: analytical accuracy of LIPOchip as reported in the paper

Study	LIPOchip version	Samples used	Total samples	Test used to verify	Number correctly detected	Comments
Alonso 2009[39]	Validation of LIPOchip (194 mutations)	Dutch samples (positive *LDLR* point mutations)	53	DNA array	51	One false-positive and one false-negative result (false-negative identified by sequencing) – based on mutational-level analysis
		Spanish samples (positive deletions in *LDLR* by QMFSP)	43	MLPA	42	One sample – detected deletions between exons varied
		Spanish random sample (positive on DNA array)	125	Re-sequencing	125	
Tejedor 2005[43]	To identify unidentified mutation that could be introduced into DNA array	Samples with negative mutations on DNA array	123	Sequencing	43	28 new mutations identified not detected previously in Spanish population
Manufacturer of LIPOchip	LIPOchip version 10 – a technical validation to evaluate its reproducibility		NR	NR	NR	For point mutations and CNV, the reproducibility obtained was 99.49% and 98.33% respectively
	Internal validation of LIPOchip version 9	Samples negative on LIPOchip	130	Sequencing		All the mutations revealed by sequencing were not present on the chip (12 new mutations on sequencing, two discrepancies with MLPA)
		Samples positive for point mutation/ negative for CNV on LIPOchip	30	MLPA	29	One discrepancy
		Point mutation and CNV positives on LIPOchip	5	Sequencing	4	
		Point mutation and CNV positives on LIPOchip	5	MLPA	4	
		Samples positive for CNV/ negative for point mutation on LIPOchip	30	Sequencing	30	
		Samples positive for CNV/ negative for point mutation on LIPOchip	30	MLPA	29	One discrepancy

CNV, copy number variation; NR, not reported.

TABLE 36 Individual study results for LDL-C

Study	FH diagnosis	Genes	Methods	Enrolled	Tested	Positive	Negative	TP	FN	FP	TN	Sensitivity	Specificity	LR+	LR–
Damgaard 2005[45]	Total		Clinical tests	408	408	317	91								
	Total	*LDLR*, *APOB*	Genetic test: screening of initial three common mutations + SSCP + sequencing + *APOB* analysis + MLPA	408	408	135	273								
			Simon Broome criteria												
	DFH					75									
	PFH					242									
	Total			408	408	317	91								
			Genetic test of those with FH from Simon Broome criteria												
	DFH				75	46	29	46		29					
	PFH				242	76	166	76		166					
	Total				317	122	195	122		195					
	Total		Genetic test of those without FH from Simon Broome criteria		91	13	78		13		78				
			Total Simon Broome criteria against reference standard					122	13	195	78	0.90	0.29	1.265185	0.337037
			Dutch criteria												
	DFH					89									
	PFH					204									
	UFH					98									
	Total				408	391	17								
			Genetic test of those with FH from the Dutch criteria												
	DFH				89	56	33								
	PFH				204	44	160								
	UFH				98	34	64								
	Total				391	134	257	134		257					
	Total		Genetic test of those without FH from the Dutch criteria		17	1	16		1		16				

Study	FH diagnosis	Genes	Methods	Enrolled	Tested	Positive	Negative	TP	FN	FP	TN	Sensitivity	Specificity	LR+	LR–
			Total Dutch criteria against reference standard					134	1	257	16	0.99	0.06	1.054388	0.126389
			MedPed criteria		408	177	231								
	Total		Genetic test of those with FH from the MedPed criteria		135	95	40	95		40					
	Total		Genetic test of those without FH from the MedPed criteria		273	82	191		82		191				
	Total		Total MedPed against reference standard					95	82	40	191	0.54	0.83	3.099576	0.560298
Civeira 2008[44]		*LDLR/ APOB/ PCSK9*	Genetic tests: LIPOchip (207 mutations in Spain) + PCR for negative results + sequencing for further negative results		825	459	366								
	DFH		Simon Broome criteria									0.59	0.93	8.428571	0.44086
	PFH											0.90	0.27	1.232877	0.37037
	Total											0.93	0.28	1.291667	0.25
	DFH		Dutch criteria									0.72	0.83	4.235294	0.337349
	Total											0.88	0.18	1.073171	0.666667
	Total		MedPed criteria									0.91	0.53	1.93617	0.169811
Widhalm 2007[47]			PCR/DGGE/sequencing – total		263	119	144								
			Adults		147	62	85								
			Children		116	57	59								
			Adults with FH		62	41	21	41	21			0.66		0.66129	
			Children with FH		57	46	11	46	11			0.81		0.807018	
Mabuchi 2005[46]	DFH[a]	*LDLR*	Genetic tests: PCR/sequencing/ Southern blot analysis		281	181	100								
			LDL-C cut-offs ≥ 4.0 mmol/l (with FH-causing mutation)		181	178	3	178	3	0	100	0.98	1.00		0.016575
			LDL-C cut-offs ≥ 4.0 mmol/l (without FH-causing mutation)		100	0	100								

DFH, definite FH; PFH, possible FH; UFH, unclassified FH.

a Diagnosis of FH was established by genetic tests in sequentially sampled first- and second-degree relatives.

Appendix 11

MOLU classification of genetic tests

Clinical Molecular Genetics Society, MOLU workload units guide version 2.2, March 2010. Available from http://www.cmgs.org /GeneralDownloads/MOLUsystemv2.2.pdf (accessed March 2011).

Band	MOLU score	General examples	Specific examples
A	1	■ All DNA extractions to include: extract > test locally; extract > DNA banking ■ DNA/sample export	
B	2	■ Single amplicon (genotyping or sequencing)	■ FraX PCR ■ Haemochromatosis ■ Factor V ■ Jak2 ■ HD (diagnostic and predictive tests) ■ Other triplet disorders in which a single PCR is required (e.g. SBMA) ■ Y deletions
C	4	■ Genotyping 2–4 amplicons ■ Sequencing: very small gene with 2–4 exons/amplicons ■ Sequencing: predictive tests, confirmations and carrier tests ■ MS-PCR ■ MLPA with no other test (including DMD) ■ Prenatal tests to include the MCC ■ One lane on Southern ■ Triplet disorders that require two PCRs (allele specific and TP-PCR) ■ Aneuploidy (to include 13, 18, 21 and X/Y) ■ Identity/paternity tests	■ CF-ARMS, CF-OLA, CF-HT ■ AS/PWS ■ FraX if Southern blotted ■ DM, Friedreich's ataxia
D	10	■ 5–19 amplicons (MLPA to count as two amplicons when part of full screen) ■ All linkage tests including UPD	■ Sequencing *MECP2* ■ DMD linkage ■ AS/PWS if linked markers used
E	15	■ 20–49 amplicons (MLPA to count as two amplicons when part of full screen)	■ Sequencing factor 8
F	25	■ 50–100 amplicons (MLPA to count as two amplicons when part of full screen)	■ Sequencing *FBN1* ■ Sequencing *BRCA1* + *BRCA2*
G	40	■ >100 amplicons	■ Sequencing a group of genes in parallel that contribute to a single report

AS/PWS, Angelman syndrome/Prader–Willi syndrome; *BRCA1*, breast cancer gene 1; *BRCA2*, breast cancer gene 2; CF-ARMS, cystic fibrosis – amplification refractory mutation system; CF-HT, cystic fibrosis – high throughput; CF-OLA, cystic fibrosis – oliogonucleotide ligation assay; DM, diabetes mellitus ; DMD, Duchenne muscular dystrophy; DNA, deoxyribonucleic acid ; FBN1, fibrillan 1; FraX PCR, Fragile X syndrome polymerase chain reaction; HD, Huntington's disease; MCC, maternal cell contamination; MECP2, methyl CpG binding protein 2; MLPA, multiplex ligation-dependant probe amplification; MS-PCR, mutagenically separated polymerase chain reaction; PCR, polymerase chain reaction; SBMA, spinal and bulbar muscular atrophy; TP-PCR, triplet repeat primed – polymerase chain reaction; UPD, uniparental disomy.

Appendix 12

Age-specific analysis for index cases only

In each of the following analyses, costs and incremental costs are rounded to the nearest whole pounds sterling. QALYs and incremental QALYs are rounded to the nearest whole QALY. ICERs are also rounded to the nearest £/QALY gained from the economic model. Therefore, the ratio of reported costs divided by reported QALYs may not always reflect an exact recalculation of the numbers from the tables. This is caused due to rounding; however, the ICERs reported are the true and exact ICERs as generated by the economic model and so minimise the impact of rounding errors on our results.

TABLE 37a Aged 15 years, index case (sequential ICERs)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	21,356,696	17,842			
Elucigene FH20_MLPA	21,615,298	17,844	Ext Dom	Ext Dom	Ext Dom
LIPOchip	22,123,539	17,847	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	22,195,239	17,847	Dominated	Dominated	Dominated
LIPOchip platform – Spain	22,277,670	17,848	920,975	7	137,963
LIPOchip_MLPA	22,374,581	17,849	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	22,446,281	17,849	Dominated	Dominated	Dominated
CGA	22,640,040	17,850	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_CGA	22,687,590	17,850	Dominated	Dominated	Dominated
LIPOchip_CGA	22,810,890	17,850	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	22,882,590	17,850	Dominated	Dominated	Dominated
LDL-C	25,788,322	17,873	3,510,651	25	142,303

Ext Dom, extendedly dominated.

TABLE 37b Age 15 years, index case (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
Elucigene FH20	21,356,696	17,842	–4,431,626	–31
LIPOchip platform – Spain	22,277,670	17,848	–3,510,651	–25
LDL-C	**25,788,322**	**17,873**		

TABLE 37c Age 15 years, index case (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	21,356,696	17,842	–1,283,344	–9	
LIPOchip platform – Spain	22,277,670	17,848	–362,370	–2	
CGA	**22,640,040**	**17,850**			
LDL-C	25,788,322	17,873	3,148,282	23	138,056

TABLE 38a Aged 30 years, index case (sequential ICERs)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	19,797,956	15,873			
Elucigene FH20_MLPA	20,047,551	15,875	Ext Dom	Ext Dom	Ext Dom
LIPOchip	20,539,419	15,877	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	20,611,119	15,877	Dominated	Dominated	Dominated
LIPOchip platform – Spain	20,686,707	15,878	Ext Dom	Ext Dom	Ext Dom
LIPOchip_MLPA	20,781,455	15,878	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	20,853,155	15,878	Dominated	Dominated	Dominated
CGA	21,040,070	15,879	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_CGA	21,087,620	15,879	Dominated	Dominated	Dominated
LIPOchip_CGA	21,210,920	15,879	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	21,282,620	15,879	Dominated	Dominated	Dominated
LDL-C	23,864,524	15,925	4,066,569	51	79,053

Ext Dom, extendedly dominated.

TABLE 38b Age 30 years, index case (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
Elucigene FH20	19,797,956	15,873	–4,066,569	–51
LDL-C	**23,864,524**	**15,925**		

TABLE 38c Age 30 years, index case (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	19,797,956	15,873	–1,242,114	–5	
CGA	**21,040,070**	**15,879**			
LDL-C	23,864,524	15,925	2,824,455	46	61,363

TABLE 39a Aged 65 years, index case (sequential ICERs)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	10,501,988	9395			
Elucigene FH20_MLPA	10,737,632	9401	Ext Dom	Ext Dom	Ext Dom
LIPOchip	11,204,139	9411	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	11,275,839	9411	Dominated	Dominated	Dominated
LIPOchip platform – Spain	11,340,826	9415	838,838	21	40,607
LIPOchip_MLPA	11,432,222	9417	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	11,503,922	9417	Dominated	Dominated	Dominated
CGA	11,680,237	9421	339,411	6	58,782
Elucigene FH20_CGA	11,727,787	9421	Dominated	Dominated	Dominated
LIPOchip_CGA	11,851,087	9421	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	11,922,787	9421	Dominated	Dominated	Dominated
LDL-C	13,140,258	9434	1,460,021	13	109,771

Ext Dom, extendedly dominated.

TABLE 39b Aged 65 years, index case (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
Elucigene FH20	10,501,988	9395	–2,638,270	–40
LIPOchip platform – Spain	11,340,826	9415	–1,799,432	–19
CGA	11,680,237	9421	–1,460,021	–13
LDL-C	**13,140,258**	**9434**		

TABLE 39c Aged 65 years, index case (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	10,501,988	9395	–1,178,249	–26	
LIPOchip platform – Spain	11,340,826	9415	–339,411	–6	
CGA	**11,680,237**	**9421**			
LDL-C	13,140,258	9434	1,460,021	13	109,771

TABLE 40a Aged 75 years, index case (sequential ICERs)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	7,645,809	6624			
Elucigene FH20_MLPA	7,832,406	6628	Ext Dom	Ext Dom	Ext Dom
LIPOchip	8,209,757	6634	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	8,281,457	6634	Dominated	Dominated	Dominated
LIPOchip platform – Spain	8,309,178	6637	663,369	12	53,738
LIPOchip_MLPA	8,388,794	6637	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	8,460,494	6637	Dominated	Dominated	Dominated
CGA	8,599,543	6640	290,365	3	84,152
Elucigene FH20_CGA	8,647,093	6640	Dominated	Dominated	Dominated
LIPOchip_CGA	8,770,393	6640	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	8,842,093	6640	Dominated	Dominated	Dominated
LDL-C	9,545,838	6641	946,294	1	1,183,172

Ext Dom, extendedly dominated.

TABLE 40b Aged 75 years, index case (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALY
Elucigene FH20	7,645,809	6624	–1,900,029	–17
LIPOchip platform – Spain	8,309,178	6637	–1,236,659	–4
CGA	8,599,543	6640	–946,294	–1
LDL-C	**9,545,838**	**6641**		

TABLE 40c Aged 75 years, index case (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALY	ICER (£/QALY)
Elucigene FH20	7,645,809	6624	–953,734	–16	
LIPOchip platform – Spain	8,309,178	6637	–290,365	–3	
CGA	**8,599,543**	**6640**			
LDL-C	9,545,838	6641	946,294	1	1,183,172

TABLE 41a Aged 85 years, index case (sequential ICERs)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	5,006,181	4036			
Elucigene FH20_MLPA	5,139,959	4038	Ext Dom	Ext Dom	Ext Dom
LIPOchip	5,421,293	4041	Ext Dom	Ext Dom	Ext Dom
LIPOchip platform – Spain	5,480,582	4042	474,401	6	78,151
Elucigene FH20_LIPOchip	5,492,993	4041	Dominated	Dominated	Dominated
LIPOchip_MLPA	5,547,511	4043	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	5,619,211	4043	Dominated	Dominated	Dominated
CGA	5,718,127	4044	237,545	2	139,999
Elucigene FH20_CGA	5,765,677	4044	Dominated	Dominated	Dominated
LIPOchip_CGA	5,888,977	4044	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	5,960,677	4044	Dominated	Dominated	Dominated
LDL-C	6,159,018	4032	Dominated	Dominated	Dominated

Ext Dom, extendedly dominated.

TABLE 41b Aged 85 years, index case (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	5,006,181	4036	–1,152,837	4	**Dominant**
LIPOchip platform – Spain	5,480,582	4042	–678,436	10	**Dominant**
CGA	5,718,127	4044	–440,891	12	**Dominant**
LDL-C	**6,159,018**	**4032**			

TABLE 41c Aged 85 years, index case (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
Elucigene FH20	5,006,181	4036	–711,946	–8
LIPOchip platform – Spain	5,480,582	4042	–237,545	–2
CGA	**5,718,127**	**4044**		

Appendix 13

Age-specific analysis for index cases and relatives

In each of the following analyses, costs and incremental costs are rounded to the nearest whole pounds sterling. QALYs and incremental QALYs are rounded to the nearest whole QALY. ICERs are also rounded to the nearest £/QALY gained from the economic model. Therefore, the ratio of reported costs divided by reported QALYs may not always reflect an exact recalculation of the numbers from the tables. This is caused due to rounding; however, the ICERs reported are the true and exact ICERs as generated by the economic model and so minimise the impact of rounding errors on our results.

TABLE 42a Analysis of index cases and relatives cascaded from index case aged 15 years

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	48,382,902	39,682			
LDL-C	49,384,423	37,360	Dominated	Dominated	Dominated
Elucigene FH20_MLPA	49,596,348	40,338	Ext	Ext Dom	Ext Dom
LIPOchip	51,840,314	41,532	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	51,912,014	41,532	Dominated	Dominated	Dominated
LIPOchip platform – Spain	52,719,939	42,031	4,337,038	2350	1846
LIPOchip_MLPA	53,046,200	42,189	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	53,117,900	42,189	Dominated	Dominated	Dominated
CGA	54,037,153	42,688	1,317,213	657	2005
Elucigene FH20_CGA	54,084,703	42,688	Dominated	Dominated	Dominated
LIPOchip_CGA	54,208,003	42,688	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	54,279,703	42,688	Dominated	Dominated	Dominated

Ext Dom, extendedly dominated.

TABLE 42b Analysis of index cases and relatives cascaded from index case aged 15 years (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	48,382,902	39,682	–1,001,521	2321	**Dominant**
LDL-C	**49,384,423**	**37,360**			
LIPOchip platform – Spain	52,719,939	42,031	3,335,516	4671	**714**
CGA	54,037,153	42,688	4,652,730	5328	**873**

TABLE 43a Analysis of index cases and relatives cascaded from index case aged 30 years

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	72,338,134	44,143			
LDL-C	72,671,492	43,013	Dominated	Dominated	Dominated
Elucigene FH20_MLPA	73,626,950	44,473	Ext Dom	Ext Dom	Ext Dom
LIPOchip	76,007,923	45,073	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	76,079,623	45,073	Dominated	Dominated	Dominated
LIPOchip platform – Spain	76,944,814	45,324	4,606,680	1181	3901
LIPOchip_MLPA	77,289,179	45,403	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	77,360,879	45,403	Dominated	Dominated	Dominated
CGA	78,337,397	45,654	1,392,583	330	4219
Elucigene FH20_CGA	78,384,947	45,654	Dominated	Dominated	Dominated
LIPOchip_CGA	78,508,247	45,654	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	78,579,947	45,654	Dominated	Dominated	Dominated

Ext Dom, extendedly dominated.

TABLE 43b Analysis of index cases and relatives cascaded from index case aged 30 years (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	72,338,134	44,143	–333,358	1130	Dominant
LDL-C	**72,671,492**	**43,013**			
LIPOchip platform – Spain	76,944,814	45,324	4,273,322	2311	1849
CGA	78,337,397	45,654	5,665,905	2641	2145

TABLE 44a Analysis of index cases and relatives cascaded from index case aged 65 years

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
LDL-C	58,704,114	34,704			
Elucigene FH20	60,370,422	36,158	1,666,308	1454	1146
Elucigene FH20_MLPA	61,804,338	36,580	Ext Dom	Ext Dom	Ext Dom
LIPOchip	64,449,077	37,346	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	64,520,777	37,346	Dominated	Dominated	Dominated
LIPOchip platform – Spain	65,496,216	37,667	5,125,794	1508	3398
LIPOchip_MLPA	65,875,433	37,768	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	65,947,133	37,768	Dominated	Dominated	Dominated
CGA	67,033,899	38,088	1,537,683	422	3647
Elucigene FH20_CGA	67,081,449	38,088	Dominated	Dominated	Dominated
LIPOchip_CGA	67,204,749	38,088	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	67,276,449	38,088	Dominated	Dominated	Dominated

Ext Dom, extendedly dominated.

TABLE 44b Analysis of index cases and relatives cascaded from index case aged 65 years (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
LDL-C	**58,704,114**	**34,704**			
Elucigene FH20	60,370,422	36,158	1,666,308	1454	**1146**
LIPOchip platform – Spain	65,496,216	37,667	6,792,102	2962	**2293**
CGA	67,033,899	38,088	8,329,786	3384	**2462**

TABLE 45a Analysis of index cases and relatives cascaded from index case aged 75 years

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
LDL-C	33,141,939	26,128			
Elucigene FH20	34,672,015	28,464	1,530,076	2336	655
Elucigene FH20_MLPA	35,813,456	29,123	Ext Dom	Ext Dom	Ext Dom
LIPOchip	37,926,532	30,319	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	37,998,232	30,319	Dominated	Dominated	Dominated
LIPOchip platform – Spain	38,751,448	30,820	4,079,432	2355	1732
LIPOchip_MLPA	39,060,413	30,978	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	39,132,113	30,978	Dominated	Dominated	Dominated
CGA	39,996,656	31,478	1,245,209	658	1891
Elucigene FH20_CGA	40,044,206	31,478	Dominated	Dominated	Dominated
LIPOchip_CGA	40,167,506	31,478	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	40,239,206	31,478	Dominated	Dominated	Dominated

Ext Dom, extendedly dominated.

TABLE 45b Analysis of index cases and relatives cascaded from index case aged 75 years (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
LDL-C	**33,141,939**	**26,128**			
Elucigene FH20	34,672,015	28,464	1,530,076	2336	**655**
LIPOchip platform – Spain	38,751,448	30,820	5,609,509	4692	**1196**
CGA	39,996,656	31,478	6,854,717	5350	**1281**

TABLE 46a Analysis of index cases and relatives cascaded from index case aged 85 years

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
LDL-C	30,692,288	17,638			
Elucigene FH20	31,577,622	18,313	885,334	675	1312
Elucigene FH20_MLPA	32,278,769	18,501	Ext Dom	Ext Dom	Ext Dom
LIPOchip	33,591,472	18,844	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	33,663,172	18,844	Dominated	Dominated	Dominated
LIPOchip platform – Spain	34,081,850	18,987	2,504,228	674	3715
LIPOchip_MLPA	34,285,059	19,032	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	34,356,759	19,032	Dominated	Dominated	Dominated
CGA	34,886,764	19,175	804,914	188	4272
Elucigene FH20_CGA	34,934,314	19,175	Dominated	Dominated	Dominated
LIPOchip_CGA	35,057,614	19,175	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	35,129,314	19,175	Dominated	Dominated	Dominated

Ext Dom, extendedly dominated.

TABLE 46b Analysis of index cases and relatives cascaded from index case aged 85 years (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
LDL-C	**30,692,288**	**17,638**			
Elucigene FH20	31,577,622	18,313	885,334	675	**1312**
LIPOchip platform – Spain	34,081,850	18,987	3,389,562	1349	**2513**
CGA	34,886,764	19,175	4,194,476	1537	**2728**

Appendix 14

One-way sensitivity analyses carried out on the base-case model

In each of the following analyses, costs and incremental costs are rounded to the nearest whole pounds sterling. QALYs and incremental QALYs are rounded to the nearest whole QALY. ICERs are also rounded to the nearest £/QALY gained from the economic model. Therefore, the ratio of reported costs divided by reported QALYs may not always reflect an exact recalculation of the numbers from the tables. This is caused due to rounding; however, the ICERs reported are the true and exact ICERs as generated by the economic model and so minimise the impact of rounding errors on our results.

The analysis presented in *Tables 47* and *48* refers to the variation in prevalence of FH in the UK. Base-case analysis uses data from Taylor and colleagues,[37] supported by the expert clinical opinion of Dr Zosia Miedzybrodzka (University of Aberdeen). The following analysis uses values ranging from 28%[79] to 52%.[41]

TABLE 47.1a Low estimate of FH prevalence in the UK (mutation positive on Simon Broome) = 28%, index cases only (sequentially presented results)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	13,834,026	13,126			
Elucigene FH20_MLPA	14,055,008	13,135	Ext Dom	Ext Dom	Ext Dom
LIPOchip	14,488,607	13,150	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	14,571,407	13,150	Dominated	Dominated	Dominated
LIPOchip platform – Spain	14,618,431	13,157	784,405	31	25,558
LIPOchip_MLPA	14,703,829	13,159	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	14,786,569	13,159	Dominated	Dominated	Dominated
CGA	14,934,997	13,166	316,566	9	36,901
Elucigene FH20_CGA	14,999,197	13,166	Dominated	Dominated	Dominated
LIPOchip_CGA	15,135,997	13,166	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	15,218,347	13,166	Dominated	Dominated	Dominated
LDL-C	17,501,754	13,195	2,566,757	29	87,175

Ext Dom, extendedly dominated.

TABLE 47.1b Low estimate of FH prevalence in the UK (mutation positive on Simon Broome) = 28%, index cases only (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
Elucigene FH20	13,834,026	13,126	–3,667,728	–69
LIPOchip platform – Spain	14,618,431	13,157	–2,883,323	–38
CGA	14,934,997	13,166	–2,566,757	–29
LDL-C	**17,501,754**	**13,195**	–	–

TABLE 47.1c Low estimate of FH prevalence in the UK (mutation positive on Simon Broome) = 28%, index cases only (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	13,834,026	13,126	–1,100,971	–39	
LIPOchip platform – Spain	14,618,431	13,157	–316,566	–9	
CGA	**14,934,997**	**13,166**	–	–	
LDL-C	17,501,754	13,195	2,566,757	29	87,175

TABLE 47.2a Low estimate of FH prevalence in the UK (mutation positive on Simon Broome) = 28%, index cases and relatives (sequentially presented results)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	42,318,489	36,311			
Elucigene FH20_MLPA	43,174,675	36,743	Ext Dom	Ext Dom	Ext Dom
LDL-C	43,704,361	34,860	Dominated	Dominated	Dominated
LIPOchip	44,762,955	37,527	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	44,845,755	37,527	Dominated	Dominated	Dominated
LIPOchip platform – Spain	45,375,409	37,855	3,056,920	1544	1979
LIPOchip_MLPA	45,613,381	37,959	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	45,696,121	37,959	Dominated	Dominated	Dominated
CGA	46,327,179	38,287	951,770	432	2205
Elucigene FH20_CGA	46,391,379	38,287	Dominated	Dominated	Dominated
LIPOchip_CGA	46,528,179	38,287	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	46,610,529	38,287	Dominated	Dominated	Dominated

Ext Dom, extendedly dominated.

TABLE 47.2b Low estimate of FH prevalence in the UK (mutation positive on Simon Broome) = 28%, index cases and relatives (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	42,318,489	36,311	–1,385,872	1451	**Dominant**
LDL-C	**43,704,361**	**34,860**			
LIPOchip platform – Spain	45,375,409	37,855	1,671,048	2996	**558**
CGA	46,327,179	38,287	2,622,819	3427	**765**

TABLE 47.2c Low estimate of FH prevalence in the UK (mutation positive on Simon Broome) = 28%, index cases and relatives (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
Elucigene FH20	42,318,489	36,311	–4,008,691	–1976
LIPOchip platform – Spain	45,375,409	37,855	–951,770	–432
CGA	**46,327,179**	**38,287**	–	–

TABLE 48.1a High estimate of FH prevalence in the UK (mutation positive on Simon Broome) = 52%, index cases (sequentially presented results)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	14,842,263	12,786			
Elucigene FH20_MLPA	15,201,307	12,802	Ext Dom	Ext Dom	Ext Dom
LIPOchip	15,903,629	12,830	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	15,954,929	12,830	Dominated	Dominated	Dominated
LIPOchip platform – Spain	16,126,407	12,843	1,284,143	57	22,530
LIPOchip_MLPA	16,251,932	12,846	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	16,303,172	12,846	Dominated	Dominated	Dominated
CGA	16,604,067	12,859	477,660	16	29,981
Elucigene FH20_CGA	16,621,017	12,859	Dominated	Dominated	Dominated
LIPOchip_CGA	16,720,467	12,859	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	16,771,317	12,859	Dominated	Dominated	Dominated
LDL-C	17,998,153	12,870	1,394,087	11	123,530

Ext Dom, extendedly dominated.

TABLE 48.1b High estimate of FH prevalence in the UK (mutation positive on Simon Broome) = 52%, index cases (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
Elucigene FH20	14,842,263	12,786	–3,155,890	–84
LIPOchip platform – Spain	16,126,407	12,843	–1,871,747	–27
CGA	16,604,067	12,859	–1,394,087	–11
LDL-C	**17,998,153**	**12,870**	–	–

TABLE 48.1c High estimate of FH prevalence in the UK (mutation positive on Simon Broome) = 52%, index cases (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	14,842,263	12,786	–1,761,804	–73	
LIPOchip platform – Spain	16,126,407	12,843	–477,660	–16	
CGA	**16,604,067**	**12,859**			
LDL-C	17,998,153	12,870	1,394,087	11	123,530

TABLE 48.2a High estimate of FH prevalence in the UK (mutation positive on Simon Broome) = 52%, index cases and relatives (sequentially presented results)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
LDL-C	44,200,760	34,535			
Elucigene FH20	45,282,603	37,273	1,081,843	2739	395
Elucigene FH20_MLPA	46,821,312	38,075	Ext Dom	Ext Dom	Ext Dom
LIPOchip	49,668,040	39,532	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	49,719,340	39,532	Dominated	Dominated	Dominated
LIPOchip platform – Spain	50,787,132	40,141	5,504,529	2868	1919
LIPOchip_MLPA	51,196,009	40,334	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	51,247,249	40,334	Dominated	Dominated	Dominated
CGA	52,444,457	40,943	1,657,325	802	2067
Elucigene FH20_CGA	52,461,407	40,943	Dominated	Dominated	Dominated
LIPOchip_CGA	52,560,857	40,943	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	52,611,707	40,943	Dominated	Dominated	Dominated

Ext Dom, extendedly dominated.

TABLE 48.2b High estimate of FH prevalence in the UK (mutation positive on Simon Broome) = 52%, index cases and relatives (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
LDL-C	**44,200,760**	**34,535**			
Elucigene FH20	45,282,603	37,273	1,081,843	2739	**395**
LIPOchip platform – Spain	50,787,132	40,141	6,586,372	5607	**1175**
CGA	52,444,457	40,943	8,243,697	6409	**1286**

TABLE 48.2c High estimate of FH prevalence in the UK (mutation positive on Simon Broome) = 52%, index cases and relatives (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
LDL-C	44,200,760	34,535	–8,243,697	–6409
Elucigene FH20	45,282,603	37,273	–7,161,854	–3670
LIPOchip platform – Spain	50,787,132	40,141	–1,657,325	–802
CGA	**52,444,457**	**40,943**	–	–

The base-case assumption in our model is that, on average, 50% of first-degree relatives of a diagnosed index case will possess the culprit genetic mutation causing FH. This, however, is an assumption based on expert opinion; therefore, in our model we need to assume some variance around this estimate. In *Tables 49* and *50* the prevalence of FH among relatives is varied by ±20%, that is, between 40% and 60%. As these results refer only to relatives, there is no impact on index cases.

TABLE 49a Low estimate of FH prevalence among relatives = 40%, index cases and relatives (sequentially presented results)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	37,215,919	32,419			
Elucigene FH20_MLPA	37,891,155	32,677	Ext Dom	Ext Dom	Ext Dom
LIPOchip	39,156,757	33,146	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	39,228,457	33,146	Dominated	Dominated	Dominated
LDL-C	39,246,248	31,607	Dominated	Dominated	Dominated
LIPOchip platform – Spain	39,627,448	33,342	2,411,529	923	2613
LIPOchip_MLPA	39,824,433	33,404	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	39,896,133	33,404	Dominated	Dominated	Dominated
CGA	40,406,451	33,600	779,003	258	3020
Elucigene FH20_CGA	40,454,001	33,600	Dominated	Dominated	Dominated
LIPOchip_CGA	40,577,301	33,600	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	40,649,001	33,600	Dominated	Dominated	Dominated

Ext Dom, extendedly dominated.

TABLE 49b Low estimate of FH prevalence among relatives = 40%, index cases and relatives (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	37,215,919	32,419	–2,030,329	812	**Dominant**
LDL-C	**39,246,248**	**31,607**			
LIPOchip platform – Spain	39,627,448	33,342	381,200	1735	**220**
CGA	40,406,451	33,600	1,160,203	1993	**582**

TABLE 49c Low estimate of FH prevalence among relatives = 40%, index cases and relatives (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
Elucigene FH20	37,215,919	32,419	–3,190,532	–1181
LIPOchip platform – Spain	39,627,448	33,342	–779,003	–258
CGA	**40,406,451**	**33,600**		

TABLE 50a High estimate of FH prevalence among relatives = 60%, index cases and relatives (sequentially presented results)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
LDL-C	49,065,143	38,227			
Elucigene FH20	50,587,294	41,583	1,522,151	3356	454
Elucigene FH20_MLPA	52,251,440	42,549	Ext Dom	Ext Dom	Ext Dom
LIPOchip	55,314,692	44,305	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	55,386,392	44,305	Dominant	Dominant	Dominant
LIPOchip platform – Spain	56,536,761	45,039	5,949,467	3456	1721
LIPOchip_MLPA	56,971,278	45,271	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	57,042,978	45,271	Dominant	Dominant	Dominant
CGA	58,304,674	46,006	1,767,913	966	1830
Elucigene FH20_CGA	58,352,224	46,006	Dominant	Dominant	Dominant
LIPOchip_CGA	58,475,524	46,006	Dominant	Dominant	Dominant
Elucigene FH20_LIPOchip_CGA	58,547,224	46,006	Dominant	Dominant	Dominant

Ext Dom, extendedly dominated.

TABLE 50b High estimate of FH prevalence among relatives = 60%, index cases and relatives (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
LDL-C	**49,065,143**	**38,227**			
Elucigene FH20	50,587,294	41,583	1,522,151	3356	**454**
LIPOchip platform – Spain	56,536,761	45,039	7,471,618	6812	**1097**
CGA	58,304,674	46,006	9,239,531	7778	**1188**

TABLE 50c High estimate of FH prevalence among relatives = 60%, index cases and relatives (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
LDL-C	49,065,143	38,227	–9,239,531	–7778
Elucigene FH20	50,587,294	41,583	–7,717,380	–4422
LIPOchip platform – Spain	56,536,761	45,039	–1,767,913	–966
CGA	**58,304,674**	**46,006**	–	–

TABLE 51.1a Reducing the cost of atorvastatin to that of generic simvastatin 80 mg, index cases (sequentially presented results)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	13,878,892	13,005			
Elucigene FH20_MLPA	14,061,700	13,016	Ext Dom	Ext Dom	Ext Dom
LIPOchip	14,432,160	13,037	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	14,503,860	13,037	Dominated	Dominated	Dominated
LIPOchip platform – Spain	14,528,702	13,045	649,809	40	16,229
LIPOchip_MLPA	14,607,407	13,048	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	14,697,107	13,048	Dominated	Dominated	Dominated
CGA	14,815,276	13,056	286,575	11	25,605
Elucigene FH20_CGA	14,862,826	13,056	Dominated	Dominated	Dominated
LIPOchip_CGA	14,986,126	13,056	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	15,057,826	13,056	Dominated	Dominated	Dominated
LDL-C	16,109,186	13,079	1,293,910	23	56,282

Ext Dom, extendedly dominated.

TABLE 51.1b Reducing the cost of atorvastatin to that of generic simvastatin 80 mg, index cases (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
Elucigene FH20	13,878,892	13,005	–2,230,294	–74
LIPOchip platform – Spain	14,528,702	13,045	–1,580,485	–34
CGA	14,815,276	13,056	–1,293,910	–23
LDL-C	**16,109,186**	**13,079**	–	–

TABLE 51.1c Reducing the cost of atorvastatin to that of generic simvastatin 80 mg, index cases (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	13,878,892	13,005	–936,384	–51	
LIPOchip platform – Spain	14,528,702	13,045	–286,575	–11	
CGA	**14,815,276**	**13,056**	–	–	
LDL-C	16,109,186	13,079	1,293,910	23	56,282

TABLE 51.2a Reducing the cost of atorvastatin to that of generic simvastatin 80 mg, index cases and relatives (sequentially presented results)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
LDL-C	39,531,598	34,744			
Elucigene FH20	39,976,768	36,653	445,170	1909	233
Elucigene FH20_MLPA	40,904,348	37,216	Ext Dom	Ext Dom	Ext Dom
LIPOchip	42,628,666	38,240	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	42,700,366	38,240	Dominated	Dominated	Dominated
LIPOchip platform – Spain	43,291,089	38,668	3,314,321	2015	1645
LIPOchip_MLPA	43,548,686	38,803	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	43,620,386	38,803	Dominated	Dominated	Dominated
CGA	44,322,437	39,231	1,031,348	563	1831
Elucigene FH20_CGA	44,369,987	39,231	Dominated	Dominated	Dominated
LIPOchip_CGA	44,493,287	39,231	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	44,564,987	39,231	Dominated	Dominated	Dominated

Ext Dom, extendedly dominated.

TABLE 51.2b Reducing the cost of atorvastatin to that of generic simvastatin 80 mg, index cases and relatives (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
LDL-C	**39,531,598**	**34,744**			
Elucigene FH20	39,976,768	36,653	445,170	1909	**233**
LIPOchip platform – Spain	43,291,089	38,668	3,759,492	3924	**958**
CGA	44,322,437	39,231	4,790,839	4487	**1068**

TABLE 51.2c Reducing the cost of atorvastatin to that of generic simvastatin 80 mg, index cases and relatives (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
LDL-C	39,531,598	34,744	–4,790,839	–4487
Elucigene FH20	39,976,768	36,653	–4,345,669	–2578
LIPOchip platform – Spain	43,291,089	38,668	–1,031,348	–563
CGA	**44,322,437**	**39,231**	–	–

TABLE 52.1a Alternative high- and low-intensity treatment scenarios (Dr Anthony Wierzbicki), index cases (sequentially reported results)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	19,077,991	13,005			
Elucigene FH20_MLPA	19,123,772	13,016	Ext Dom	Ext Dom	Ext Dom
LIPOchip platform – Spain	19,237,573	13,045	Ext Dom	Ext Dom	Ext Dom
LIPOchip	19,245,144	13,037	Dominated	Dominated	Dominated
LIPOchip_MLPA	19,283,365	13,048	Ext Dom	Ext Dom	Ext Dom
LDL-C	19,311,875	13,079	233,884	74	3161
Elucigene FH20_LIPOchip	19,316,844	13,037	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_MLPA	19,355,065	13,048	Dominated	Dominated	Dominated
CGA	19,387,121	13,056	Dominated	Dominated	Dominated
Elucigene FH20_CGA	19,434,671	13,056	Dominated	Dominated	Dominated
LIPOchip_CGA	19,557,971	13,056	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	19,629,671	13,056	Dominated	Dominated	Dominated

Ext Dom, extendedly dominated.

TABLE 52.1b Alternative high- and low-intensity treatment scenarios (Dr Anthony Wierzbicki), index cases (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
Elucigene FH20	19,077,991	13,005	–233,884	–74
LDL–C	**19,311,875**	**13,079**	–	–

TABLE 52.1c Alternative high- and low-intensity treatment scenarios (Dr Anthony Wierzbicki), index cases (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	19,077,991	13,005	–309,130	–51	
LDL-C	19,311,875	13,079	–75,246	23	Dominant
CGA	**19,387,121**	**13,056**			

TABLE 52.2a Alternative high- and low-intensity treatment scenarios (Dr Anthony Wierzbicki), index cases and relatives (sequentially reported results)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
LDL-C	47,524,644	34,744			
Elucigene FH20	50,339,916	36,653	2,815,272	1909	1475
Elucigene FH20_MLPA	51,234,495	37,216	Ext Dom	Ext Dom	Ext Dom
LIPOchip	52,898,822	38,240	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	52,970,522	38,240	Dominated	Dominated	Dominated
LIPOchip platform – Spain	53,536,172	38,668	3,196,256	2015	1586
LIPOchip_MLPA	53,785,842	38,803	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	53,857,542	38,803	Dominated	Dominated	Dominated
CGA	54,534,518	39,231	998,347	563	1773
Elucigene FH20_CGA	54,582,068	39,231	Dominated	Dominated	Dominated
LIPOchip_CGA	54,705,368	39,231	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	54,777,068	39,231	Dominated	Dominated	Dominated

Ext Dom, extendedly dominated.

TABLE 52.2b Alternative high- and low-intensity treatment scenarios (Dr Anthony Wierzbicki), index cases and relatives (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
LDL-C	**47,524,644**	**34,744**			
Elucigene FH20	50,339,916	36,653	2,815,272	1909	**1475**
LIPOchip platform – Spain	53,536,172	38,668	6,011,528	3924	**1532**
CGA	54,534,518	39,231	7,009,875	4487	**1562**

TABLE 52.2c Alternative high- and low-intensity treatment scenarios (Dr Anthony Wierzbicki), index cases and relatives (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
LDL-C	47,524,644	34,744	–7,009,875	–4487
Elucigene FH20	50,339,916	36,653	–4,194,603	–2578
LIPOchip platform – Spain	53,536,172	38,668	–998,347	–563
CGA	**54,534,518**	**39,231**	–	–

The analyses presented in *Table 53* relate to the potential treatment of negative-testing relatives. This value is assumed to be 10% in the model. As this is purely an assumption based on author opinion, this value is varied between 0% and 50% in sensitivity analysis. As this has no effect on the results for index cases alone, results are presented only for index cases and relatives combined. It is assumed that if negative relatives are treated then their treatment of choice will be low-intensity statin therapy as defined for the base-case model.

TABLE 53.1a Impact of reducing proportion of negative-testing relatives receiving treatment to 0%, index cases and relatives (sequentially presented results)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	42,251,638	33,421			
LDL-C	42,709,251	31,523	Dominated	Dominated	Dominated
Elucigene FH20_MLPA	43,364,673	33,981	Ext Dom	Ext Dom	Ext Dom
LIPOchip	45,426,111	34,999	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	45,497,811	34,999	Dominated	Dominated	Dominated
LIPOchip platform – Spain	46,229,444	35,425	3,977,806	2004	1985
LIPOchip_MLPA	46,531,587	35,559	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	46,603,287	35,559	Dominated	Dominated	Dominated
CGA	47,446,247	35,985	1,216,803	560	2172
Elucigene FH20_CGA	47,493,797	35,985	Dominated	Dominated	Dominated
LIPOchip_CGA	47,617,097	35,985	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	47,688,797	35,985	Dominated	Dominated	Dominated

Ext Dom, extendedly dominated.

TABLE 53.1b Impact of reducing proportion of negative-testing relatives receiving treatment to 0%, index cases and relatives (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental effects	ICER (£/QALY)
Elucigene FH20	42,251,638	33,421	–457,614	1898	**Dominant**
LDL-C	**42,709,251**	**31,523**			
LIPOchip platform – Spain	46,229,444	35,425	3,520,193	3902	**902**
CGA	47,446,247	35,985	4,736,995	4462	**1062**

TABLE 53.1c Impact of reducing proportion of negative-testing relatives receiving treatment to 0%, index cases and relatives (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
Elucigene FH20	42,251,638	33,421	–5,194,609	–2564
LIPOchip platform – Spain	46,229,444	35,425	–1,216,803	–560
CGA	**47,446,247**	**35,985**	–	–

TABLE 53.2a Impact of increasing proportion of negative-testing relatives receiving treatment to 50%, index cases and relatives (sequentially presented results)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	47,853,372	49,583			
LDL-C	48,566,941	47,630	Dominated	Dominated	Dominated
Elucigene FH20_MLPA	48,895,157	50,158	Ext Dom	Ext Dom	Ext Dom
LIPOchip	50,827,075	51,204	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	50,898,775	51,204	Dominated	Dominated	Dominated
LIPOchip platform – Spain	51,576,271	51,641	3,722,899	2059	1808
LIPOchip_MLPA	51,861,300	51,780	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	51,933,000	51,780	Dominated	Dominated	Dominated
CGA	52,721,823	52,217	1,145,552	575	1991
Elucigene FH20_CGA	52,769,373	52,217	Dominated	Dominated	Dominated
LIPOchip_CGA	52,892,673	52,217	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	52,964,373	52,217	Dominated	Dominated	Dominated

Ext Dom, extendedly dominated.

TABLE 53.2b Impact of increasing proportion of negative-testing relatives receiving treatment to 50%, index cases and relatives (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	47,853,372	49,583	–713,569	1953	**Dominant**
LDL-C	**48,566,941**	**47,630**			
LIPOchip platform – Spain	51,576,271	51,641	3,009,331	4011	**750**
CGA	52,721,823	52,217	4,154,883	4587	**906**

TABLE 53.2c Impact of increasing proportion of negative-testing relatives receiving treatment to 50%, index cases and relatives (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
Elucigene FH20	47,853,372	49,583	–4,868,451	–2634
LIPOchip in Spain	51,576,271	51,641	–1,145,552	–575
CGA	**52,721,823**	**52,217**		

Base-case analysis assumes that all test-negative index cases will require some treatment. The justification for this assumption is that all these patients will have elevated lipids and will thus be at increased risk of CHD. However, it is possible that these patients could be managed effectively using diet and exercise interventions, the evaluation of which is beyond the scope of this report. Therefore, to assess the impact of this assumption on our results, *Table 54* presents the analysis assuming an extreme case scenario in which none of the test-negative index cases will receive treatment. Index cases are therefore not followed up clinically in this scenario.

TABLE 54.1a Test-negative index cases do not receive treatment, index cases (sequentially presented results)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	8,205,446	1967			
Elucigene FH20_MLPA	8,863,412	2514	Ext Dom	Ext Dom	Ext Dom
LIPOchip	10,097,620	3509	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	10,169,320	3509	Dominated	Dominated	Dominated
LIPOchip platform – Spain	10,555,189	3925	Ext Dom	Ext Dom	Ext Dom
LIPOchip_MLPA	10,748,025	4057	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	10,819,725	4057	Dominated	Dominated	Dominated
CGA	11,316,921	4473	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_CGA	11,364,471	4473	Dominated	Dominated	Dominated
LIPOchip_CGA	11,487,771	4473	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	11,559,471	4473	Dominated	Dominated	Dominated
LDL-C	16,140,001	10,152	7,934,555	8185	969

Ext Dom, extendedly dominated.

TABLE 54.1b Test-negative index cases do not receive treatment, index cases (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
Elucigene FH20	8,205,446	1967	–7,934,555	–8185
LDL-C	**16,140,001**	**10,152**	–	–

TABLE 54.1c Test-negative index cases do not receive treatment, index cases (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	8,205,446	1967	–3,111,475	–2506	
CGA	**11,316,921**	**4473**	–	–	
LDL-C	16,140,001	10,152	4,823,079	5679	849

TABLE 54.2a Test-negative index cases do not receive treatment, index cases and relatives (sequentially presented results)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	37,385,060	25,614			
Elucigene FH20_MLPA	38,871,740	26,714	Ext Dom	Ext Dom	Ext Dom
LIPOchip	41,612,394	28,713	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip	41,684,094	28,713	Dominated	Dominated	Dominated
LDL-C	42,342,607	31,817	4,957,547	6202	799
LIPOchip platform – Spain	42,699,624	29,548	Dominated	Dominated	Dominated
LIPOchip_MLPA	43,091,514	29,812	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_MLPA	43,163,214	29,812	Dominated	Dominated	Dominated
CGA	44,290,071	30,648	Dominated	Dominated	Dominated
Elucigene FH20_CGA	44,337,621	30,648	Dominated	Dominated	Dominated
LIPOchip_CGA	44,460,921	30,648	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	44,532,621	30,648	Dominated	Dominated	Dominated

Ext Dom, extendedly dominated.

TABLE 54.2b Test-negative index cases do not receive treatment, index cases and relatives (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	37,385,060	25,614	–4,957,547	–6202	
LDL-C	**42,342,607**	**31,817**	–	–	**–**

TABLE 54.2c Test-negative index cases do not receive treatment, index cases and relatives (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	37,385,060	25,614	–6,905,011	–5033	
LDL-C	42,342,607	31,817	–1,947,464	1169	Dominant
CGA	**44,290,071**	**30,648**	–	–	

TABLE 55.1a Cost of MOLU (high value) = £40, index cases (sequentially presented results)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	14,242,370	13,005			
Elucigene FH20_MLPA	14,529,221	13,016	Ext Dom	Ext Dom	Ext Dom
LIPOchip	15,101,529	13,037	Ext Dom	Ext Dom	Ext Dom
LIPOchip platform – Spain	15,154,374	13,045	912,004	40	22,777
Elucigene FH20_LIPOchip	15,197,129	13,037	Dominated	Dominated	Dominated
LIPOchip_MLPA	15,378,300	13,048	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	15,473,900	13,048	Dominated	Dominated	Dominated
CGA	15,688,212	13,056	533,838	11	47,698
Elucigene FH20_CGA	15,751,612	13,056	Dominated	Dominated	Dominated
LIPOchip_CGA	15,916,012	13,056	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	16,011,612	13,056	Dominated	Dominated	Dominated
LDL-C	17,678,183	13,079	1,989,970	23	86,558

Ext Dom, extendedly dominated.

TABLE 55.1b Cost of MOLU (high value) = £40, index cases (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
Elucigene FH20	14,242,370	13,005	–3,435,812	–74
LIPOchip platform – Spain	15,154,374	13,045	–2,523,808	–34
CGA	15,688,212	13,056	–1,989,970	–23
LDL–C	**17,678,183**	**13,079**	–	–

TABLE 55.1c Cost of MOLU (high value) = £40, index cases (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	14,242,370	13,005	–1,445,842	–51	
LIPOchip platform – Spain	15,154,374	13,045	–533,838	–11	
CGA	**15,688,212**	**13,056**			
LDL-C	17,678,183	13,079	1,989,970	23	86,558

TABLE 55.2a Cost of MOLU (high value) = £40, index cases and relatives (sequentially presented results)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	43,444,427	36,653			
LDL-C	43,880,789	34,744	Dominated	Dominated	Dominated
Elucigene FH20_MLPA	44,566,239	37,216	Ext Dom	Ext Dom	Ext Dom
LIPOchip	46,656,350	38,240	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	46,751,950	38,240	Dominated	Dominated	Dominated
LIPOchip platform – Spain	47,343,602	38,668	3,899,175	2015	1935
LIPOchip_MLPA	47,768,083	38,803	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	47,863,683	38,803	Dominated	Dominated	Dominated
CGA	48,712,402	39,231	1,368,800	563	2430
Elucigene FH20_CGA	48,775,802	39,231	Dominated	Dominated	Dominated
LIPOchip_CGA	48,940,202	39,231	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	49,035,802	39,231	Dominated	Dominated	Dominated

Ext Dom, extendedly dominated.

TABLE 55.2b Cost of MOLU (high value) = £40, index cases and relatives (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	43,444,427	36,653	–436,362	1909	**Dominant**
LDL-C	**43,880,789**	**34,744**			
LIPOchip platform – Spain	47,343,602	38,668	3,462,813	3924	**883**
CGA	48,712,402	39,231	4,831,613	4487	**1077**

TABLE 55.2c Cost of MOLU (high value) = £40, index cases and relatives (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
Elucigene FH20	43,444,427	36,653	–5,267,975	–2578
LIPOchip platform – Spain	47,343,602	38,668	–1,368,800	–563
CGA	**48,712,402**	**39,231**		

TABLE 56.1a Cost of MOLU (low value) = £20, index cases (sequentially presented results)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	14,142,370	13,005			
Elucigene FH20_MLPA	14,395,661	13,016	Ext Dom	Ext Dom	Ext Dom
LIPOchip	14,881,529	13,037	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	14,929,329	13,037	Dominated	Dominated	Dominated
LIPOchip_MLPA	15,129,780	13,048	987,410	43	23,108
LIPOchip platform – Spain	15,154,374	13,045	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_MLPA	15,177,580	13,048	Dominated	Dominated	Dominated
CGA	15,368,212	13,056	238,432	9	28,038
Elucigene FH20_CGA	15,399,912	13,056	Dominated	Dominated	Dominated
LIPOchip_CGA	15,482,112	13,056	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	15,529,912	13,056	Dominated	Dominated	Dominated
LDL-C	17,678,183	13,079	2,309,970	23	100,474

Ext Dom, extendedly dominated.

TABLE 56.1b Cost of MOLU (low value) = £20, index cases (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
Elucigene FH20	14,142,370	13,005	–3,535,812	–74
LIPOchip_MLPA	15,129,780	13,048	–2,548,403	–31
CGA	15,368,212	13,056	–2,309,970	–23
LDL-C	**17,678,183**	**13,079**	–	–

TABLE 56.1c Cost of MOLU (low value) = £20, index cases (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	14,142,370	13,005	–1,225,842	–51	
LIPOchip_MLPA	15,129,780	13,048	–238,432	–9	
CGA	15,368,212	13,056		–	
LDL-C	17,678,183	13,079	2,309,970	23	100,477

TABLE 56.2a Cost of MOLU (low value) = £20, index cases and relatives (sequentially presented results)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	43,299,542	36,653			
LDL-C	43,880,789	34,744	Dominated	Dominated	Dominated
Elucigene FH20_MLPA	44,375,300	37,216	Ext Dom	Ext Dom	Ext Dom
LIPOchip	46,356,258	38,240	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	46,404,058	38,240	Dominated	Dominated	Dominated
LIPOchip platform – Spain	47,254,017	38,668	Ext Dom	Ext Dom	Ext Dom
LIPOchip_MLPA	47,426,976	38,803	4,127,434	2150	1920
Elucigene FH20_LIPOchip_MLPA	47,474,776	38,803	Dominated	Dominated	Dominated
CGA	48,290,322	39,231	863,346	428	2017
Elucigene FH20_CGA	48,322,022	39,231	Dominated	Dominated	Dominated
LIPOchip_CGA	48,404,222	39,231	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	48,452,022	39,231	Dominated	Dominated	Dominated

Ext Dom, extendedly dominated.

TABLE 56.2b Cost of MOLU (low value) = £20, index cases and relatives (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	43,299,542	36,653	–581,247	1909	**Dominant**
LDL-C	**43,880,789**	**34,744**			
LIPOchip_MLPA	47,426,976	38,803	3,546,187	4059	**874**
CGA	48,290,322	39,231	4,409,532	4487	**983**

TABLE 56.2c Cost of MOLU (low value) = £20, index cases and relatives (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
Elucigene FH20	43,299,542	36,653	–4,990,780	–2578
LIPOchip_MLPA	47,426,976	38,803	–863,346	–428
CGA	**48,290,322**	**39,231**		

TABLE 57a Cascade testing of first- and second-degree relatives only (sequentially presented results)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	37,712,894	32,096			
Elucigene FH20_MLPA	38,506,088	32,440	Ext Dom	Ext Dom	Ext Dom
LDL-C	39,319,481	30,973	Dominated	Dominated	Dominated
LIPOchip	39,986,115	33,066	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	40,057,815	33,066	Dominated	Dominated	Dominated
LIPOchip platform – Spain	40,546,431	33,328	2,833,537	1232	2299
LIPOchip_MLPA	40,771,748	33,411	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	40,843,448	33,411	Dominated	Dominated	Dominated
CGA	41,443,392	33,673	896,961	344	2604
Elucigene FH20_CGA	41,490,942	33,673	Dominated	Dominated	Dominated
LIPOchip_CGA	41,614,242	33,673	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	41,685,942	33,673	Dominated	Dominated	Dominated

Ext Dom, extendedly dominated.

TABLE 57b Cascade testing of first- and second-degree relatives only (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	37,712,894	32,096	–1,606,587	1123	**Dominant**
LDL-C	**39,319,481**	**30,973**			
LIPOchip platform – Spain	40,546,431	33,328	1,226,950	2355	**521**
CGA	41,443,392	33,673	2,123,911	2700	**787**

TABLE 57c Cascade testing of first- and second-degree relatives only (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
Elucigene FH20	37,712,894	32,096	–3,730,498	–1577
LIPOchip platform – Spain	40,546,431	33,328	–896,961	–344
CGA	**41,443,392**	**33,673**		

The sensitivity analyses in *Table 58* refers to not cascade testing from index cases in whom a genetic mutation has not been identified.

TABLE 58.1a No cascade testing of relatives of index test-negative cases, index cases (sequentially presented results)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	14,192,370	13,005			
Elucigene FH20_MLPA	14,462,441	13,016	Ext Dom	Ext Dom	Ext Dom
LIPOchip	14,991,529	13,037	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	15,063,229	13,037	Dominated	Dominated	Dominated
LIPOchip platform – Spain	15,154,374	13,045	962,004	40	24,025
LIPOchip_MLPA	15,254,040	13,048	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	15,325,740	13,048	Dominated	Dominated	Dominated
CGA	15,528,212	13,056	373,838	11	33,402
Elucigene FH20_CGA	15,575,762	13,056	Dominated	Dominated	Dominated
LIPOchip_CGA	15,699,062	13,056	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	15,770,762	13,056	Dominated	Dominated	Dominated
LDL-C	17,678,183	13,079	2,149,970	23	93,518

Ext Dom, extendedly dominated.

TABLE 58.1b No cascade testing of relatives of index test-negative cases, index cases (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
Elucigene FH20	14,192,370	13,005	–3,485,812	–74
LIPOchip platform – Spain	15,154,374	13,045	–2,523,808	–34
CGA	15,528,212	13,056	–2,149,970	–23
LDL-C	**17,678,183**	**13,079**	–	–

TABLE 58.1c No cascade testing of relatives of index test-negative cases, index cases (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	14,192,370	13,005	–1,335,842	–51	
LIPOchip platform – Spain	15,154,374	13,045	–373,838	–11	
CGA	**15,528,212**	**13,056**			
LDL-C	17,678,183	13,079	2,149,970	23	93,518

TABLE 58.2a No cascade testing of relatives of index test-negative cases, index cases and relatives (sequentially presented results)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	21,378,104	18,468			
Elucigene FH20_MLPA	23,648,479	20,000	Ext Dom	Ext Dom	Ext Dom
LIPOchip	27,813,741	22,785	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	27,885,441	22,785	Dominated	Dominated	Dominated
LIPOchip platform – Spain	29,496,425	23,949	Ext Dom	Ext Dom	Ext Dom
LIPOchip_MLPA	30,076,556	24,317	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	30,148,256	24,317	Dominated	Dominated	Dominated
CGA	31,870,568	25,481	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_CGA	31,918,118	25,481	Dominated	Dominated	Dominated
LIPOchip_CGA	32,041,418	25,481	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	32,113,118	25,481	Dominated	Dominated	Dominated
LDL-C	38,100,678	29,965	16,722,574	11,497	1455

Ext Dom, extendedly dominated.

TABLE 58.2b No cascade testing of relatives of index test-negative cases, index cases and relatives (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
Elucigene FH20	21,378,104	18,468	–16,722,574	–11,497
LDL-C	**38,100,678**	**29,965**		

TABLE 58.2c No cascade testing of relatives of index test-negative cases, index cases and relatives (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	21,378,104	18,468	–10,492,464	–7012	
CGA	**31,870,568**	**25,481**			
LDL-C	38,100,678	29,965	6,230,110	4484	1389

Hadfeld and colleagues[66] estimate that 69% of index cases and also 69% of qualifiable relatives will agree to genetic testing being carried out. There will not be any implications here for index cases alone and therefore the results in *Table 59* are for index and relative cases combined only.

TABLE 59a Adjusting proportions of index cases and relatives agreeing to be tested to 69% (sequentially presented results)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
LDL-C	54,528,198	43,548			
Elucigene FH20	55,623,568	46,562	1,095,370	3015	363
Elucigene FH20_MLPA	57,168,909	47,433	Ext Dom	Ext Dom	Ext Dom
LIPOchip	60,016,199	49,016	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	60,087,899	49,016	Dominated	Dominated	Dominated
LIPOchip platform – Spain	61,148,000	49,678	5,524,433	3116	1773
LIPOchip_MLPA	61,553,981	49,887	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	61,625,681	49,887	Dominated	Dominated	Dominated
CGA	62,797,109	50,549	1,649,109	871	1893
Elucigene FH20_CGA	62,844,659	50,549	Dominated	Dominated	Dominated
LIPOchip_CGA	62,967,959	50,549	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	63,039,659	50,549	Dominated	Dominated	Dominated

Ext Dom, extendedly dominated.

TABLE 59b Adjusting proportions of index cases and relatives agreeing to be tested to 69% (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
LDL-C	**54,528,198**	**43,548**			
Elucigene FH20	55,623,568	46,562	1,095,370	3015	**363**
LIPOchip platform – Spain	61,148,000	49,678	6,619,802	6131	**1080**
CGA	62,797,109	50,549	8,268,912	7002	**1181**

TABLE 59c Adjusting proportions of index cases and relatives agreeing to be tested to 69% (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
LDL-C	54,528,198	43,548	–8,268,912	–7002
Elucigene FH20	55,623,568	46,562	–7,173,542	–3987
LIPOchip platform – Spain	61,148,000	49,678	–1,649,109	–871
CGA	**62,797,109**	**50,549**		

TABLE 60.1a Assume discount rate for costs and benefits = 0%, index cases (sequentially produced results)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	27,204,825	20,571			
Elucigene FH20_MLPA	27,611,712	20,594	Ext Dom	Ext Dom	Ext Dom
LIPOchip	28,389,507	20,636	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	28,461,207	20,636	Dominated	Dominated	Dominated
LIPOchip platform – Spain	28,656,305	20,654	1,451,480	84	17,377
LIPOchip_MLPA	28,788,833	20,660	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	28,860,533	20,660	Dominated	Dominated	Dominated
CGA	29,166,959	20,678	510,654	23	21,872
Elucigene FH20_CGA	29,214,509	20,678	Dominated	Dominated	Dominated
LIPOchip_CGA	29,337,809	20,678	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	29,409,509	20,678	Dominated	Dominated	Dominated
LDL_C	32,978,473	20,728	3,811,514	50	75,678

Ext Dom, extendedly dominated.

TABLE 60.1b Assume discount rate for costs and benefits = 0%, index cases (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
Elucigene FH20	27,204,825	20,571	–5,773,648	–157
LIPOchip platform – Spain	28,656,305	20,654	–4,322,169	–74
CGA	29,166,959	20,678	–3,811,514	–50
LDL-C	**32,978,473**	**20,728**	–	–

TABLE 60.1c Assume discount rate for costs and benefits = 0%, index cases (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	27,204,825	20,571	–1,962,134	–107	
LIPOchip platform – Spain	28,656,305	20,654	–510,654	–23	
CGA	**29,166,959**	**20,678**	–	–	
LDL-C	32,978,473	20,728	3,811,514	50	75,678

TABLE 60.2a Assume discount rate for costs and benefits = 0%, index cases and relatives (sequentially produced results)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	80,370,221	58,348			
LDL-C	80,740,629	55,359	Dominated	Dominated	Dominated
Elucigene FH20_MLPA	82,281,317	59,248	Ext Dom	Ext Dom	Ext Dom
LIPOchip	85,793,478	60,883	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	85,865,178	60,883	Dominated	Dominated	Dominated
LIPOchip platform – Spain	87,203,180	61,566	6,832,959	3218	2123
LIPOchip_MLPA	87,697,014	61,782	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	87,768,714	61,782	Dominated	Dominated	Dominated
CGA	89,218,043	62,466	2,014,863	899	2240
Elucigene FH20_CGA	89,265,593	62,466	Dominated	Dominated	Dominated
LIPOchip_CGA	89,388,893	62,466	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	89,460,593	62,466	Dominated	Dominated	Dominated

Ext Dom, extendedly dominated.

TABLE 60.2b Assume discount rate for costs and benefits = 0%, index cases and relatives (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	80,370,221	58,348	–370,048	2990	**Dominant**
LDL-C	**80,740,629**	**55,359**			
LIPOchip platform – Spain	87,203,180	61,566	6,462,911	6208	**1041**
CGA	89,218,043	62,466	8,477,774	7107	**1193**

TABLE 60.2c Assume discount rate for costs and benefits = 0%, index cases and relatives (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
Elucigene FH20	80,370,221	58,348	–8,814,822	–4117
LIPOchip platform – Spain	87,203,180	61,566	–2,014,863	–899
CGA	**89,218,043**	**62,466**		

TABLE 61.1a Assume discount rate for costs and benefits = 6%, index cases (sequentially produced results)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	10,029,010	10,117			
Elucigene FH20_MLPA	10,248,696	10,125	Ext Dom	Ext Dom	Ext Dom
LIPOchip	10,686,196	10,138	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	10,757,896	10,138	Dominated	Dominated	Dominated
LIPOchip platform – Spain	10,810,758	10,143	781,748	26	30,023
LIPOchip_MLPA	10,898,322	10,145	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	10,970,022	10,145	Dominated	Dominated	Dominated
CGA	11,134,212	10,151	323,454	7	44,442
Elucigene FH20_CGA	11,181,762	10,151	Dominated	Dominated	Dominated
LIPOchip_CGA	11,305,062	10,151	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	11,376,762	10,151	Dominated	Dominated	Dominated
LDL-C	12,668,695	10,165	1,534,483	14	109,720

Ext Dom, extendedly dominated.

TABLE 61.1b Assume discount rate for costs and benefits = 6%, index cases (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
Elucigene FH20	10,029,010	10,117	–2,639,685	–47
LIPOchip platform – Spain	10,810,758	10,143	–1,857,937	–21
CGA	11,134,212	10,151	–1,534,483	–14
LDL-C	**12,668,695**	**10,165**	–	–

TABLE 61.1c Assume discount rate for costs and benefits = 6%, index cases (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	10,029,010	10,117	–1,105,202	–33	
LIPOchip platform – Spain	10,810,758	10,143	–323,454	–7	
CGA	**11,134,212**	**10,151**	–	–	
LDL-C	12,668,695	10,165	1,534,483	14	109,720

TABLE 61.2a Assume discount rate for costs and benefits = 6%, index cases and relatives (sequentially produced results)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	31,278,303	28,428			
LDL-C	31,745,080	26,934	Dominated	Dominated	Dominated
Elucigene FH20_MLPA	32,102,865	28,865	Ext Dom	Ext Dom	Ext Dom
LIPOchip	33,639,915	29,658	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	33,711,615	29,658	Dominated	Dominated	Dominated
LIPOchip platform – Spain	34,224,064	29,989	2,945,761	1561	1887
LIPOchip_MLPA	34,456,917	30,094	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	34,528,617	30,094	Dominated	Dominated	Dominated
CGA	35,152,394	30,426	928,329	436	2127
Elucigene FH20_CGA	35,199,944	30,426	Dominated	Dominated	Dominated
LIPOchip_CGA	35,323,244	30,426	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	35,394,944	30,426	Dominated	Dominated	Dominated

Ext Dom, extendedly dominated.

TABLE 61.2b Assume discount rate for costs and benefits = 6%, index cases and relatives (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	31,278,303	28,428	–466,777	1494	**Dominant**
LDL-C	**31,745,080**	**26,934**			
LIPOchip platform – Spain	34,224,064	29,989	2,478,984	3055	**811**
CGA	35,152,394	30,426	3,407,313	3492	**976**

TABLE 61.2c Assume discount rate for costs and benefits = 6%, index cases and relatives (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
Elucigene FH20	31,278,303	28,428	–3,874,090	–1998
LIPOchip platform – Spain	34,224,064	29,989	–928,329	–436
CGA	**35,152,394**	**30,426**		

The base-case analysis assumes that there will be no reduction in the cost of next-generation sequencing. Clinical advice is that there will be a reduction in cost; however, we are unsure as to how much that reduction will be in practice. *Table 62* presents the results of the sensitivity analysis assuming that next-generation sequencing costs will reduce by 40% into the future.

TABLE 62.1a Forty per cent reduction in costs of next-generation sequencing, index cases (sequentially presented results)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	14,192,370	13,005			
Elucigene FH20_MLPA	14,462,441	13,016	Ext Dom	Ext Dom	Ext Dom
LIPOchip	14,991,529	13,037	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	15,063,229	13,037	Dominated	Dominated	Dominated
LIPOchip platform – Spain	15,154,374	13,045	Ext Dom	Ext Dom	Ext Dom
LIPOchip_MLPA	15,254,040	13,048	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	15,325,740	13,048	Dominated	Dominated	Dominated
CGA	15,372,212	13,056	1,179,842	51	23,029
Elucigene FH20_CGA	15,444,878	13,056	Dominated	Dominated	Dominated
LIPOchip_CGA	15,587,834	13,056	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	15,659,534	13,056	Dominated	Dominated	Dominated
LDL-C	17,678,183	13,079	2,305,970	23	100,303

Ext Dom, extendedly dominated.

TABLE 62.1b Forty per cent reduction in costs of next-generation sequencing, index cases (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
Elucigene FH20	14,192,370	13,005	–3,485,812	–74
CGA	15,372,212	13,056	–2,305,970	–23
LDL-C	**17,678,183**	**13,079**		

TABLE 62.1c Forty per cent reduction in costs of next-generation sequencing, index cases (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	14,192,370	13,005	–1,179,842	–51	
CGA	**15,372,212**	**13,056**			
LDL-C	17,678,183	13,079	2,305,970	23	100,303

TABLE 62.2a Forty per cent reduction in costs of next-generation sequencing, index cases and relatives (sequentially presented results)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	43,371,985	36,653			
LDL-C	43,880,789	34,744	Dominated	Dominated	Dominated
Elucigene FH20_MLPA	44,470,770	37,216	Ext Dom	Ext Dom	Ext Dom
LIPOchip	46,506,304	38,240	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	46,578,004	38,240	Dominated	Dominated	Dominated
LIPOchip platform – Spain	47,298,810	38,668	Ext Dom	Ext Dom	Ext Dom
LIPOchip_MLPA	47,597,529	38,803	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	47,669,229	38,803	Dominated	Dominated	Dominated
CGA	48,345,362	39,231	4,973,377	2578	1929
Elucigene FH20_CGA	48,418,028	39,231	Dominated	Dominated	Dominated
LIPOchip_CGA	48,560,984	39,231	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	48,632,684	39,231	Dominated	Dominated	Dominated

Ext Dom, extendedly dominated.

TABLE 62.2b Forty per cent reduction in costs of next-generation sequencing, index cases and relatives (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	43,371,985	36,653	–508,805	1909	**Dominant**
LDL-C	**43,880,789**	**34,744**			
CGA	48,345,362	39,231	4,464,573	4487	**995**

TABLE 62.2c Forty per cent reduction in costs of next-generation sequencing, index cases and relatives (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
Elucigene FH20	43,371,985	36,653	–4,973,377	–2578
CGA	**48,345,362**	**39,231**		

Table 63 details the effect of a high value for the sensitivity of Elucigene FH20. This is the highest estimate from the clinical effectiveness review and is 52%.[38]

TABLE 63.1a High estimate for sensitivity of Elucigene FH20 = 0.52, index cases (sequentially presented results)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	14,336,524	13,013			
Elucigene FH20_MLPA	14,604,854	13,024	Ext Dom	Ext Dom	Ext Dom
LIPOchip	14,991,529	13,037	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	15,054,529	13,037	Dominated	Dominated	Dominated
LIPOchip platform – Spain	15,154,374	13,045	817,851	33	25,012
LIPOchip_MLPA	15,254,040	13,048	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	15,317,040	13,048	Dominated	Dominated	Dominated
CGA	15,528,212	13,056	373,838	11	33,402
Elucigene FH20_CGA	15,562,712	13,056	Dominated	Dominated	Dominated
LIPOchip_CGA	15,699,062	13,056	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	15,762,062	13,056	Dominated	Dominated	Dominated
LDL-C	17,678,183	13,079	2,149,970	23	93,518

Ext Dom, extendedly dominated.

TABLE 63.1b High estimate for sensitivity of Elucigene FH20 = 0.52, index cases (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
Elucigene FH20	14,336,524	13,013	–3,341,659	–67
LIPOchip platform – Spain	15,154,374	13,045	–2,523,808	–34
CGA	15,528,212	13,056	–2,149,970	–23
LDL-C	**17,678,183**	**13,079**		

TABLE 63.1c High estimate for sensitivity of Elucigene FH20 = 0.52, index cases (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	14,336,524	13,013	–1,191,689	–44	
LIPOchip platform – Spain	15,154,374	13,045	–373,838	–11	
CGA	**15,528,212**	**13,056**			
LDL-C	17,678,183	13,079	2,149,970	23	93,518

TABLE 63.2a High estimate for sensitivity of Elucigene FH20 = 0.52, index cases and relatives (sequentially presented results)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
LDL-C	43,880,789	34,744			
Elucigene FH20	44,059,813	37,022	179,023	2278	79
Elucigene FH20_MLPA	45,156,858	37,586	Ext Dom	Ext Dom	Ext Dom
LIPOchip	46,506,304	38,240	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	46,569,304	38,240	Dominated	Dominated	Dominated
LIPOchip platform – Spain	47,298,810	38,668	3,238,997	1645	1968
LIPOchip_MLPA	47,597,529	38,803	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	47,660,529	38,803	Dominated	Dominated	Dominated
CGA	48,501,362	39,231	1,202,552	563	2135
Elucigene FH20_CGA	48,535,862	39,231	Dominated	Dominated	Dominated
LIPOchip_CGA	48,672,212	39,231	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	48,735,212	39,231	Dominated	Dominated	Dominated

Ext Dom, extendedly dominated.

TABLE 63.2b High estimate for sensitivity of Elucigene FH20 = 0.52, index cases and relatives (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
LDL-C	**43,880,789**	**34,744**			
Elucigene FH20	44,059,813	37,022	179,023	2278	**79**
LIPOchip platform – Spain	47,298,810	38,668	3,418,020	3924	**871**
CGA	48,501,362	39,231	4,620,573	4487	**1030**

TABLE 63.2c High estimate for sensitivity of Elucigene FH20 = 0.52, index cases and relatives (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
LDL-C	43,880,789	34,744	–4,620,573	–4487
Elucigene FH20	44,059,813	37,022	–4,441,549	–2209
LIPOchip platform – Spain	47,298,810	38,668	–1,202,552	–563
CGA	**48,501,362**	**39,231**		

Table 64 presents the results of sensitivity analysis in which the lower limit of the sensitivity of Elucigene FH20 is used (i.e. a sensitivity of 0.286, taken from Hooper and colleagues[36]).

TABLE 64.1a Low estimate for sensitivity of Elucigene FH20 = 0.286, index cases (sequentially presented results)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	13,916,450	12,991			
Elucigene FH20_MLPA	14,189,881	13,002	Ext Dom	Ext Dom	Ext Dom
LIPOchip	14,991,529	13,037	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	15,080,029	13,037	Dominated	Dominated	Dominated
LIPOchip platform – Spain	15,154,374	13,045	1,237,924	54	22,884
LIPOchip_MLPA	15,254,040	13,048	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	15,342,480	13,048	Dominated	Dominated	Dominated
CGA	15,528,212	13,056	373,838	11	33,402
Elucigene FH20_CGA	15,600,962	13,056	Dominated	Dominated	Dominated
LIPOchip_CGA	15,699,062	13,056	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	15,787,112	13,056	Dominated	Dominated	Dominated
LDL-C	17,678,183	13,079	2,149,970	23	93,518

Ext Dom, extendedly dominated.

TABLE 64.1b Low estimate for sensitivity of Elucigene FH20 = 0.286, index cases (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
Elucigene FH20	13,916,450	12,991	–3,761,732	–88
LIPOchip platform – Spain	15,154,374	13,045	–2,523,808	–34
CGA	15,528,212	13,056	–2,149,970	–23
LDL-C	**17,678,183**	**13,079**		

TABLE 64.1c Low estimate for sensitivity of Elucigene FH20 = 0.286, index cases (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	13,916,450	12,991	–1,611,762	–65	
LIPOchip platform – Spain	15,154,374	13,045	–373,838	–11	
CGA	**15,528,212**	**13,056**			
LDL-C	17,678,183	13,079	2,149,970	23	93,518

TABLE 64.2a Low estimate for sensitivity of Elucigene FH20 = 0.286, index cases and relatives (sequentially presented results)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	42,055,432	35,946			
Elucigene FH20_MLPA	43,157,577	36,509	Ext Dom	Ext Dom	Ext Dom
LDL-C	43,880,789	34,744	Dominated	Dominated	Dominated
LIPOchip	46,506,304	38,240	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	46,594,804	38,240	Dominated	Dominated	Dominated
LIPOchip platform – Spain	47,298,810	38,668	5,243,377	2722	1926
LIPOchip_MLPA	47,597,529	38,803	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	47,685,969	38,803	Dominated	Dominated	Dominated
CGA	48,501,362	39,231	1,202,552	563	2135
Elucigene FH20_CGA	48,574,112	39,231	Dominated	Dominated	Dominated
LIPOchip_CGA	48,672,212	39,231	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	48,760,262	39,231	Dominated	Dominated	Dominated

Ext Dom, extendedly dominated.

TABLE 64.2b Low estimate for sensitivity of Elucigene FH20 = 0.286, index cases and relatives (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	42,055,432	35,946	–1,825,357	1202	Dominant
LDL-C	**43,880,789**	**34,744**			
LIPOchip platform – Spain	47,298,810	38,668	3,418,020	3924	871
CGA	48,501,362	39,231	4,620,573	4487	1030

TABLE 64.2c Low estimate for sensitivity of Elucigene FH20 = 0.286, index cases and relatives (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
Elucigene FH20	42,055,432	35,946	–6,445,390	–3285
LIPOchip platform – Spain	47,298,810	38,668	–1,202,552	–563
CGA	**48,501,362**	**39,231**		

Tables 65 and *66* report deterministic sensitivity analyses for LIPOchip sensitivity. The high value is taken from Stef and colleagues[42] and the low value is taken from Callaway and colleagues.[40]

TABLE 65.1a High estimate for sensitivity of LIPOchip = 0.945, index cases (sequentially presented results)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	14,192,370	13,005			
Elucigene FH20_MLPA	14,462,411	13,016	Ext Dom	Ext Dom	Ext Dom
LIPOchip platform – Spain	15,149,123	13,045	Ext Dom	Ext Dom	Ext Dom
LIPOchip	15,279,477	13,051	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	15,351,177	13,051	Dominated	Dominated	Dominated
CGA	15,528,212	13,056	Ext Dom	Ext Dom	Ext Dom
LIPOchip_MLPA[a]	15,538,448	13,063	1,346,078	57	23,452
Elucigene FH20_CGA	15,575,762	13,056	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_MLPA	15,610,148	13,063	Dominated	Dominated	Dominated
LIPOchip_CGA	15,672,512	13,056	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	15,744,212	13,056	Dominated	Dominated	Dominated
LDL-C	17,678,183	13,079	2,139,735	17	127,161

Ext Dom, extendedly dominated.
a Results for this extreme scenario are not reliable as they would lead to a sensitivity of LIPOchip_MLPA of > 1.

TABLE 65.1b High estimate for sensitivity of LIPOchip = 0.945, index cases (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
Elucigene FH20	14,192,370	13,005	–3,485,812	–74
LIPOchip_MLPA[a]	15,538,448	13,063	–2,139,735	–17
LDL-C	**17,678,183**	**13,079**		

a Results for this extreme scenario are not reliable as they would lead to a sensitivity of LIPOchip_MLPA of > 1.

TABLE 65.1c High estimate for sensitivity of LIPOchip = 0.945, index cases (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	14,192,370	13,005	–1,335,842	–51	
CGA	**15,528,212**	**13,056**			
LIPOchip_MLPA[a]	15,538,448	13,063	10,235	6	1661
LDL-C	17,678,183	13,079	2,149,970	23	93,518

a Results for this extreme scenario are not reliable as they would lead to a sensitivity of LIPOchip_MLPA of > 1.

TABLE 65.2a High estimate for sensitivity of LIPOchip = 0.945, index cases and relatives (sequentially presented results)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	43,371,985	36,653			
LDL-C	43,880,789	34,744	Dominated	Dominated	Dominated
Elucigene FH20_MLPA	44,470,770	37,216	Ext Dom	Ext Dom	Ext Dom
LIPOchip platform – Spain	47,293,559	38,668	Ext Dom	Ext Dom	Ext Dom
LIPOchip	47,880,247	38,978	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	47,951,947	38,978	Dominated	Dominated	Dominated
CGA	48,501,362	39,231	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_CGA	48,548,912	39,231	Dominated	Dominated	Dominated
LIPOchip_CGA	48,645,662	39,231	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	48,717,362	39,231	Dominated	Dominated	Dominated
LIPOchip_MLPA[a]	48,967,932	39,541	5,595,947	2888	1937
Elucigene FH20_LIPOchip_MLPA	49,039,632	39,541	Dominated	Dominated	Dominated

Ext Dom, extendedly dominated.

a Results for this extreme scenario are not reliable as they would lead to a sensitivity of LIPOchip_MLPA of > 1.

TABLE 65.2b High estimate for sensitivity of LIPOchip = 0.945, index cases and relatives (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	43,371,985	36,653	–508,805	1909	**Dominant**
LDL-C	**43,880,789**	**34,744**			
LIPOchip_MLPA[a]	48,967,932	39,541	5,087,143	4797	**1060**

a Results for this extreme scenario are not reliable as they would lead to a sensitivity of LIPOchip_MLPA of > 1.

TABLE 65.2c High estimate for sensitivity of LIPOchip = 0.945, index cases and relatives (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	43,371,985	36,653	–5,129,377	–2578	
CGA	**48,501,362**	**39,231**	–	–	
LIPOchip_MLPA[a]	48,967,932	39,541	466,570	310	1504

a Results for this extreme scenario are not reliable as they would lead to a sensitivity of LIPOchip_MLPA of > 1.

TABLE 66.1a Low estimate for sensitivity of LIPOchip = 0.33, index cases (sequentially presented results)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
LIPOchip	14,175,438	12,995			
Elucigene FH20	14,192,370	13,005	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	14,247,138	12,995	Dominated	Dominated	Dominated
LIPOchip_MLPA	14,447,909	13,006	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_MLPA	14,462,441	13,016	287,002	21	13,523
Elucigene FH20_LIPOchip_MLPA	14,519,669	13,006	Dominated	Dominated	Dominated
LIPOchip platform – Spain	15,169,148	13,045	706,707	29	24,497
CGA	15,528,212	13,056	359,064	11	32,082
Elucigene FH20_CGA	15,575,762	13,056	Dominated	Dominated	Dominated
LIPOchip_CGA	15,773,762	13,056	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	15,845,912	13,056	Dominated	Dominated	Dominated
LDL-C	17,678,183	13,079	2,149,970	23	93,518

Ext Dom, extendedly dominated.

TABLE 66.1b Low estimate for sensitivity of LIPOchip = 0.33, index cases (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
LIPOchip	14,175,438	12,995	–3,502,744	–84
Elucigene FH20_MLPA	14,462,441	13,016	–3,215,742	–63
LIPOchip platform – Spain	15,169,148	13,045	–2,509,034	–34
CGA	15,528,212	13,056	–2,149,970	–23
LDL-C	**17,678,183**	**13,079**		

TABLE 66.1c Low estimate for sensitivity of LIPOchip = 0.33, index cases (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
LIPOchip	14,175,438	12,995	–1,352,774	–61	
Elucigene FH20_MLPA	14,462,441	13,016	–1,065,771	–40	
LIPOchip platform – Spain	15,169,148	13,045	–359,064	–11	
CGA	**15,528,212**	**13,056**			
LDL-C	17,678,183	13,079	2,149,970	23	93,518

TABLE 66.2a Low estimate for sensitivity of LIPOchip = 0.33, index cases and relatives (sequentially presented results)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
LIPOchip	42,612,324	36,148			
Elucigene FH20_LIPOchip	42,684,024	36,148	Dominated	Dominated	Dominated
Elucigene FH20	43,371,985	36,653	Ext Dom	Ext Dom	Ext Dom
LIPOchip_MLPA	43,713,509	36,711	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	43,785,269	36,711	Dominated	Dominated	Dominated
LDL-C	43,880,789	34,744	Dominated	Dominated	Dominated
Elucigene FH20_MLPA	44,470,770	37,216	1,858,445	1068	1740
LIPOchip platform – Spain	47,313,584	38,668	2,842,814	1452	1958
CGA	48,501,362	39,231	1,187,778	563	2109
Elucigene FH20_CGA	48,548,912	39,231	Dominated	Dominated	Dominated
LIPOchip_CGA	48,746,912	39,231	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	48,819,062	39,231	Dominated	Dominated	Dominated

Ext Dom, extendedly dominated.

TABLE 66.2b Low estimate for sensitivity of LIPOchip = 0.33, index cases and relatives (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
LIPOchip	42,612,324	36,148	–1,268,465	1404	**Dominant**
LDL-C	**43,880,789**	**34,744**			
Elucigene FH20_MLPA	44,470,770	37,216	589,980	2472	**239**
LIPOchip platform – Spain	47,313,584	38,668	3,432,794	3924	**875**
CGA	48,501,362	39,231	4,620,573	4487	**1030**

TABLE 66.2c Low estimate for sensitivity of LIPOchip = 0.33, index cases (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
LIPOchip	42,612,324	36,148	–5,889,038	–3083
Elucigene FH20_MLPA	44,470,770	37,216	–4,030,592	–2015
LIPOchip platform – Spain	47,313,584	38,668	–1,187,778	–563
CGA	**48,501,362**	**39,231**		

Table 67 details the results of sensitivity analysis using the upper bound of the CI for the sensitivity of LDL-C among relatives from Starr and colleagues.[49] This applies only to relatives and therefore results for index cases alone will not change in this analysis.

TABLE 67a High estimate for sensitivity of LDL-C in relatives = 0.679 (aged 50 years), index cases and relatives (sequentially presented results)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	48,545,084	40,457			
Elucigene FH20_MLPA	49,368,304	40,817	Ext Dom	Ext Dom	Ext Dom
LDL-C	50,043,807	39,276	Dominated	Dominated	Dominated
LIPOchip	50,902,913	41,473	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	50,974,613	41,473	Dominated	Dominated	Dominated
LIPOchip platform – Spain	51,486,042	41,747	2,940,959	1290	2280
LIPOchip_MLPA	51,718,572	41,833	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	51,790,272	41,833	Dominated	Dominated	Dominated
CGA	52,413,029	42,107	926,987	361	2571
Elucigene FH20_CGA	52,460,579	42,107	Dominated	Dominated	Dominated
LIPOchip_CGA	52,583,879	42,107	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	52,655,579	42,107	Dominated	Dominated	Dominated

Ext Dom, extendedly dominated.

TABLE 67b High estimate for sensitivity of LDL-C in relatives = 0.679 (aged 50 years), index cases and relatives (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	48,545,084	40,457	–1,498,723	1181	**Dominant**
LDL-C	**50,043,807**	**39,276**			
LIPOchip platform – Spain	51,486,042	41,747	1,442,235	2471	**584**
CGA	52,413,029	42,107	2,369,222	2832	**837**

TABLE 67c High estimate for sensitivity of LDL-C in relatives = 0.679 (aged 50 years), index cases and relatives (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
Elucigene FH20	48,545,084	40,457	–3,867,946	–1651
LIPOchip platform – Spain	51,486,042	41,747	–926,987	–361
CGA	**52,413,029**	**42,107**		

Table 68 details the results of sensitivity analysis using the lower bound of the CI for the sensitivity of LDL-C among relatives from Starr and colleagues.[49] This applies only to relatives and therefore results for index cases alone will not change in this analysis.

TABLE 68a Low estimate for sensitivity of LDL-C in relatives = 0.469 (aged 50 years), index cases and relatives (sequentially presented results)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
LDL-C	38,314,283	30,629			
Elucigene FH20	38,699,584	33,199	385,301	2570	150
Elucigene FH20_MLPA	40,047,263	33,946	Ext Dom	Ext Dom	Ext Dom
LIPOchip	42,535,238	35,304	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	42,606,938	35,304	Dominated	Dominated	Dominated
LIPOchip platform – Spain	43,516,854	35,872	4,817,270	2673	1802
LIPOchip_MLPA	43,875,357	36,051	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	43,947,057	36,051	Dominated	Dominated	Dominated
CGA	44,968,300	36,619	1,451,446	747	1942
Elucigene FH20_CGA	45,015,850	36,619	Dominated	Dominated	Dominated
LIPOchip_CGA	45,139,150	36,619	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	45,210,850	36,619	Dominated	Dominated	Dominated

Ext Dom, extendedly dominated.

TABLE 68b Low estimate for sensitivity of LDL-C in relatives = 0.469 (aged 50 years), index cases and relatives (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
LDL-C	**38,314,283**	**30,629**			
Elucigene FH20	38,699,584	33,199	385,301	2570	**150**
LIPOchip platform – Spain	43,516,854	35,872	5,202,571	5243	**992**
CGA	44,968,300	36,619	6,654,018	5990	**1111**

TABLE 68c Low estimate for sensitivity of LDL-C in relatives = 0.469 (aged 50 years), index cases and relatives (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
LDL-C	38,314,283	30,629	–6,654,018	–5990
Elucigene FH20	38,699,584	33,199	–6,268,716	–3420
LIPOchip platform – Spain	43,516,854	35,872	–1,451,446	–747
CGA	**44,968,300**	**36,619**		

Table 69 presents analysis for the high estimate of the sensitivity of LDL-C in index cases (high value = 1), assuming that if the LDL-C test result is negative then the index case is a true negative; however, this is not always the case in reality.

TABLE 69.1a High estimate for sensitivity of LDL-C among index patients = 1, index cases (sequentially presented results)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	14,192,370	13,005			
Elucigene FH20_MLPA	14,462,441	13,016	Ext Dom	Ext Dom	Ext Dom
LIPOchip	14,991,529	13,037	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	15,063,229	13,037	Dominated	Dominated	Dominated
LIPOchip platform – Spain	15,154,374	13,045	962,004	40	24,025
LIPOchip_MLPA	15,254,040	13,048	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	15,325,740	13,048	Dominated	Dominated	Dominated
CGA	15,528,212	13,056	373,838	11	33,402
Elucigene FH20_CGA	15,575,762	13,056	Dominated	Dominated	Dominated
LIPOchip_CGA	15,699,062	13,056	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	15,770,762	13,056	Dominated	Dominated	Dominated
LDL-C	17,857,701	13,089	2,329,489	32	72,493

Ext Dom, extendedly dominated.

TABLE 69.1b High estimate for sensitivity of LDL-C among index patients = 1, index cases (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
Elucigene FH20	14,192,370	13,005	–3,665,331	–83
LIPOchip platform – Spain	15,154,374	13,045	–2,703,327	–43
CGA	15,528,212	13,056	–2,329,489	–32
LDL-C	**17,857,701**	**13,089**		

TABLE 69.1c High estimate for sensitivity of LDL-C among index patients = 1, index cases (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
Elucigene FH20	14,192,370	13,005	–1,335,842	–51
LIPOchip platform – Spain	15,154,374	13,045	–373,838	–11
CGA	**15,528,212**	**13,056**		

TABLE 69.2a High estimate for sensitivity of LDL-C among index patients = 1, index cases and relatives (sequentially presented results)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	43,371,985	36,653			
LDL-C	44,060,308	34,753	Dominated	Dominated	Dominated
Elucigene FH20_MLPA	44,470,770	37,216	Ext Dom	Ext Dom	Ext Dom
LIPOchip	46,506,304	38,240	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	46,578,004	38,240	Dominated	Dominated	Dominated
LIPOchip platform – Spain	47,298,810	38,668	3,926,825	2015	1949
LIPOchip_MLPA	47,597,529	38,803	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	47,669,229	38,803	Dominated	Dominated	Dominated
CGA	48,501,362	39,231	1,202,552	563	2135
Elucigene FH20_CGA	48,548,912	39,231	Dominated	Dominated	Dominated
LIPOchip_CGA	48,672,212	39,231	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	48,743,912	39,231	Dominated	Dominated	Dominated

Ext Dom, extendedly dominated.

TABLE 69.2b High estimate for sensitivity of LDL-C among index patients = 1, index cases (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	43,371,985	36,653	–688,323	1900	Dominant
LDL-C	**44,060,308**	**34,753**			
LIPOchip platform – Spain	47,298,810	38,668	3,238,502	3915	827
CGA	48,501,362	39,231	4,441,054	4478	992

TABLE 69.2c High estimate for sensitivity of LDL-C among index patients = 1, index cases (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
Elucigene FH20	43,371,985	36,653	–5,129,377	–2578
LIPOchip platform – Spain	47,298,810	38,668	–1,202,552	–563
CGA	**48,501,362**	**39,231**		

Table 70 presents analysis for the low estimate of sensitivity of LDL-C among index cases (low value = 0.54,[45] MedPed criteria).

TABLE 70.1a Low estimate for sensitivity of LDL-C among index patients = 0.54, index cases (sequentially presented results)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	14,192,370	13,005			
Elucigene FH20_MLPA	14,462,441	13,016	Ext Dom	Ext Dom	Ext Dom
LIPOchip	14,991,529	13,037	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	15,063,229	13,037	Dominated	Dominated	Dominated
LIPOchip platform – Spain	15,154,374	13,045	962,004	40	24,025
LIPOchip_MLPA	15,254,040	13,048	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	15,325,740	13,048	Dominated	Dominated	Dominated
CGA	15,528,212	13,056	373,838	11	33,402
Elucigene FH20_CGA	15,575,762	13,056	Dominated	Dominated	Dominated
LIPOchip_CGA	15,699,062	13,056	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	15,770,762	13,056	Dominated	Dominated	Dominated
LDL-C	17,031,916	13,047	Dominated	Dominated	Dominated

Ext Dom, extendedly dominated.

TABLE 70.1b Low estimate for sensitivity of LDL-C among index patients = 0.54, index cases (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	14,192,370	13,005	–2,839,546	–41	
LIPOchip platform – Spain	15,154,374	13,045	–1,877,542	–1	
CGA	15,528,212	13,056	–1,503,704	10	Dominant
LDL-C	**17,031,916**	**13,047**			

TABLE 70.1c Low estimate for sensitivity of LDL-C among index patients = 0.54, index cases (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
Elucigene FH20	14,192,370	13,005	–1,335,842	–51
LIPOchip platform – Spain	15,154,374	13,045	–373,838	–11
CGA	**15,528,212**	**13,056**		

TABLE 70.2a Low estimate for sensitivity of LDL-C among index patients = 0.54, index cases and relatives (sequentially presented results)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
LDL-C	43,234,523	34,711			
Elucigene FH20	43,371,985	36,653	137,462	1942	71
Elucigene FH20_MLPA	44,470,770	37,216	Ext Dom	Ext Dom	Ext Dom
LIPOchip	46,506,304	38,240	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	46,578,004	38,240	Dominated	Dominated	Dominated
LIPOchip platform – Spain	47,298,810	38,668	3,926,825	2015	1949
LIPOchip_MLPA	47,597,529	38,803	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	47,669,229	38,803	Dominated	Dominated	Dominated
CGA	48,501,362	39,231	1,202,552	563	2135
Elucigene FH20_CGA	48,548,912	39,231	Dominated	Dominated	Dominated
LIPOchip_CGA	48,672,212	39,231	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	48,743,912	39,231	Dominated	Dominated	Dominated

Ext Dom, extendedly dominated.

TABLE 70.2b Low estimate for sensitivity of LDL-C among index patients = 0.54, index cases (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
LDL-C	**43,234,523**	**34,711**			
Elucigene FH20	43,371,985	36,653	137,462	1942	**71**
LIPOchip platform – Spain	47,298,810	38,668	4,064,287	3957	**1027**
CGA	48,501,362	39,231	5,266,839	4520	**1165**

TABLE 70.2c Low estimate for sensitivity of LDL-C among index patients = 0.54, index cases (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
LDL-C	43,234,523	34,711	–5,266,839	–4520
Elucigene FH20	43,371,985	36,653	–5,129,377	–2578
LIPOchip platform – Spain	47,298,810	38,668	–1,202,552	–563
CGA	**48,501,362**	**39,231**		

Table 71 details the results of sensitivity analysis using the upper bound of the CI for the specificity of LDL-C among relatives (values are taken from Starr and colleagues[49] and apply only to index cases and relatives together). Results refer to relatives of a 50-year-old index case as in the base-case model.

TABLE 71a High estimate for specificity of LDL-C among relatives = 0.87, index cases and relatives (sequentially presented results)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	41,972,619	35,492			
LDL-C	42,213,642	33,361	Dominated	Dominated	Dominated
Elucigene FH20_MLPA	43,145,947	36,117	Ext Dom	Ext Dom	Ext Dom
LIPOchip	45,316,985	37,253	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	45,388,685	37,253	Dominated	Dominated	Dominated
LIPOchip platform – Spain	46,166,129	37,728	4,193,510	2236	1875
LIPOchip_MLPA	46,482,753	37,878	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	46,554,453	37,878	Dominated	Dominated	Dominated
CGA	47,443,224	38,353	1,277,095	625	2043
Elucigene FH20_CGA	47,490,774	38,353	Dominated	Dominated	Dominated
LIPOchip_CGA	47,614,074	38,353	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	47,685,774	38,353	Dominated	Dominated	Dominated

Ext Dom, extendedly dominated.

TABLE 71b High estimate for specificity of LDL-C among relatives = 0.87, index cases and relatives (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	41,972,619	35,492	–241,023	2131	Dominant
LDL-C	**42,213,642**	**33,361**			
LIPOchip platform – Spain	46,166,129	37,728	3,952,486	4367	905
CGA	47,443,224	38,353	5,229,581	4992	1048

TABLE 71C High estimate for specificity of LDL-C among relatives = 0.87, index case and relatives (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
Elucigene FH20	41,972,619	35,492	–5,470,605	–2861
LIPOchip platform – Spain	46,166,129	37,728	–1,277,095	–625
CGA	**47,443,224**	**38,353**		

Table 72 details the results of sensitivity analysis using the lower bound of the CI for the specificity of LDL-C among relatives (values are taken from Starr and colleagues[49] and apply only to index cases and relatives together). Results refer to relatives of a 50-year-old index case as in the base-case model.

TABLE 72a Low estimate for specificity of LDL-C among relatives = 0.80, index cases and relatives (sequentially presented results)

Test strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	45,013,836	38,015			
LDL-C	45,836,823	36,367	Dominated	Dominated	Dominated
Elucigene FH20_MLPA	46,025,161	38,506	Ext Dom	Ext Dom	Ext Dom
LIPOchip	47,901,711	39,398	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip	48,973,411	39,398	Dominated	Dominated	Dominated
LIPOchip platform – Spain	48,627,764	39,771	3,613,928	1755	2059
LIPOchip_MLPA	48,905,476	39,888	Ext Dom	Ext Dom	Ext Dom
Elucigene FH20_LIPOchip_MLPA	48,977,176	39,888	Dominated	Dominated	Dominated
CGA	49,742,857	40,261	1,115,093	491	2273
Elucigene FH20_CGA	49,790,407	40,261	Dominated	Dominated	Dominated
LIPOchip_CGA	49,913,707	40,261	Dominated	Dominated	Dominated
Elucigene FH20_LIPOchip_CGA	49,985,407	40,261	Dominated	Dominated	Dominated

Ext Dom, extendedly dominated.

TABLE 72b Low estimate for specificity of LDL-C among relatives = 0.80, index cases and relatives (relevant comparison LDL-C)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elucigene FH20	45,013,836	38,015	–822,988	1,648	Dominant
LDL-C	**45,836,823**	**36,367**			
LIPOchip platform – Spain	48,627,764	39,771	2,790,941	3403	820
CGA	49,742,857	40,261	3,906,033	3894	1003

TABLE 72c Low estimate for specificity of LDL-C among relatives = 0.80, index cases and relatives (relevant comparison CGA)

Test	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs
Elucigene FH20	45,013,836	38,015	–4,729,021	–2246
LIPOchip platform – Spain	48,627,764	39,771	–1,115,093	–491
CGA	**49,742,857**	**40,261**		

Appendix 15

Cost-effectiveness acceptability curves for each age subgroup

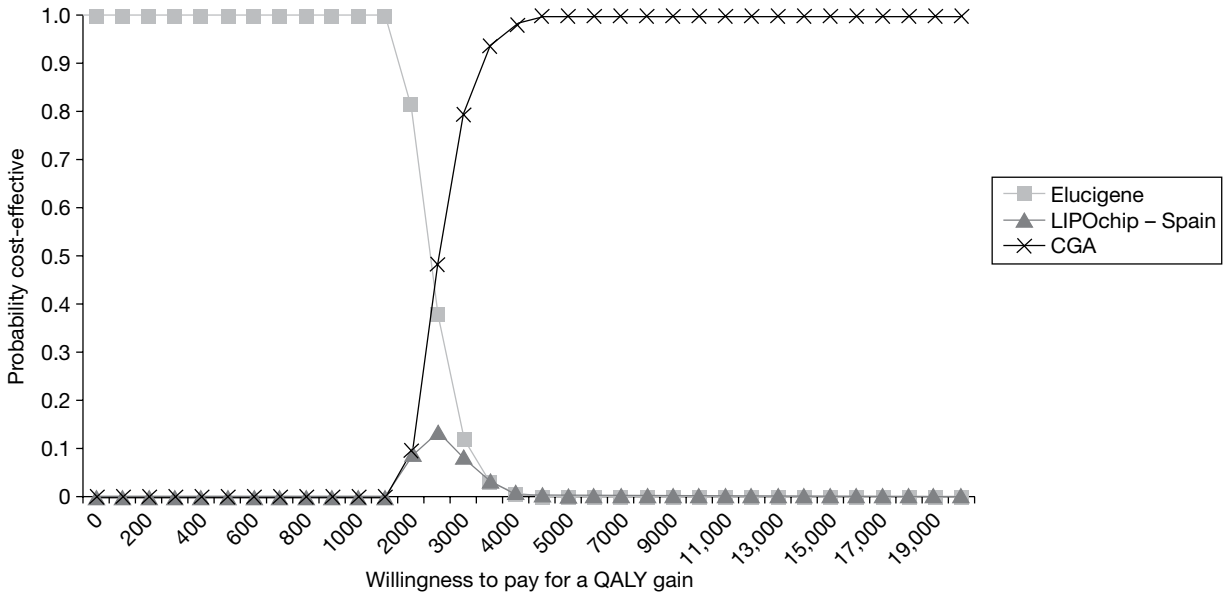

FIGURE 13 Cost-effectiveness acceptability curve: age 15 years, index case.

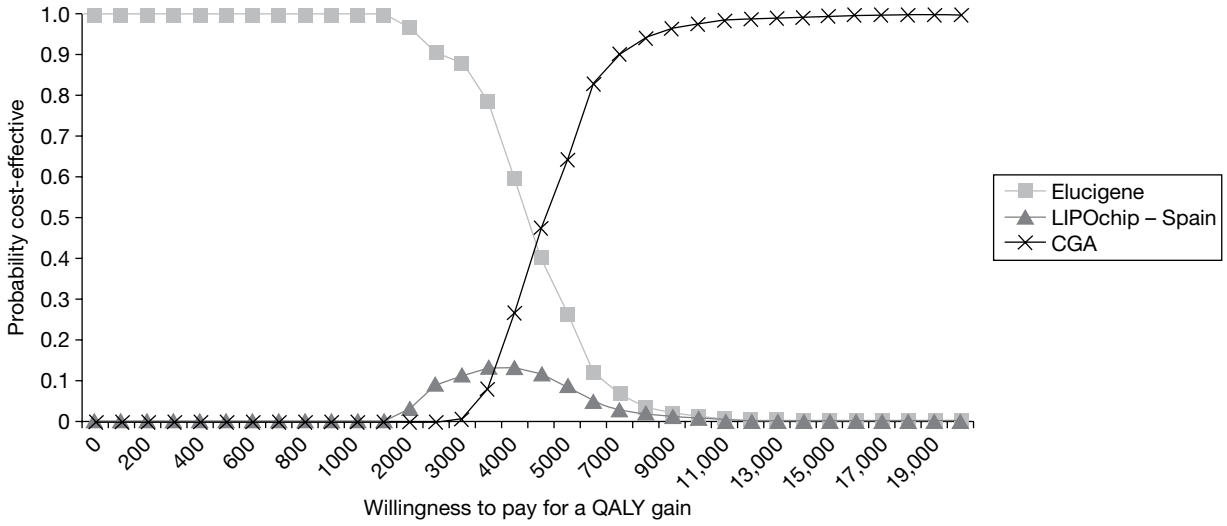

FIGURE 14 Cost-effectiveness acceptability curve: age 30 years, index case.

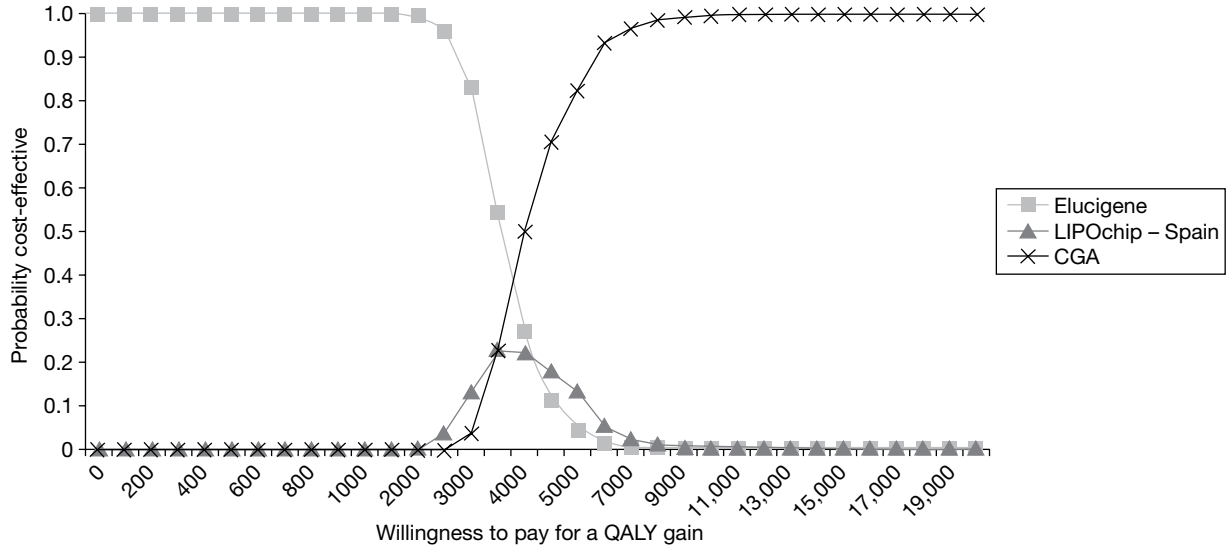

FIGURE 15 Cost-effectiveness acceptability curve: age 65 years, index case.

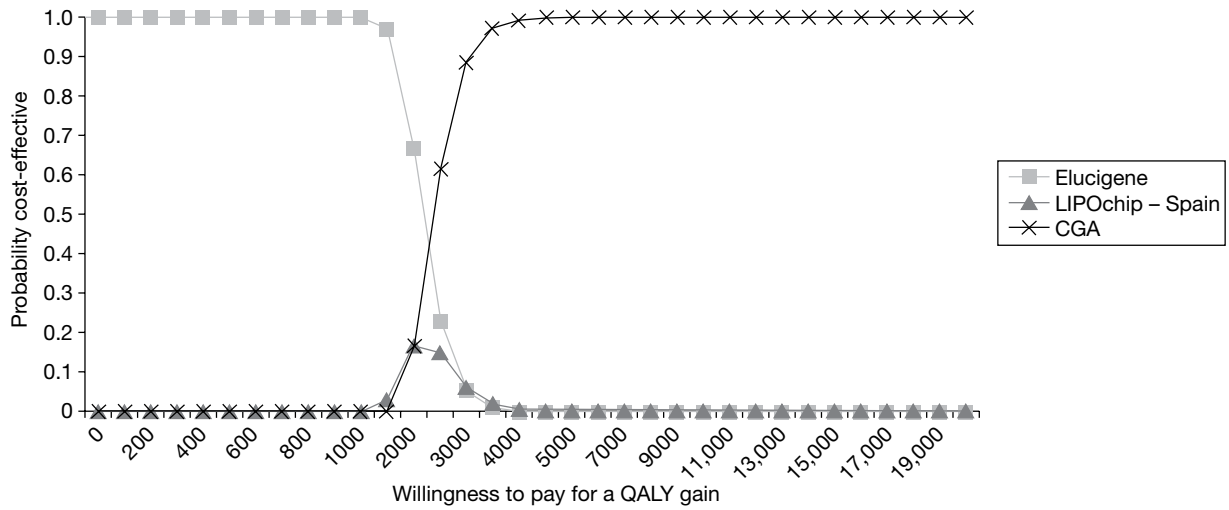

FIGURE 16 Cost-effectiveness acceptability curve: age 75 years, index case.

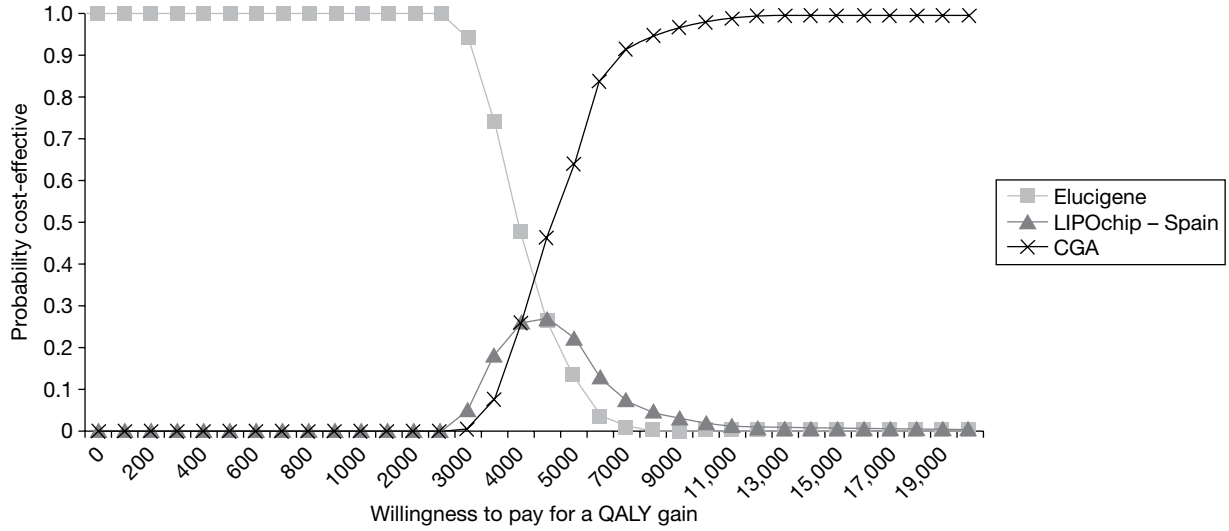

FIGURE 17 Cost-effectiveness acceptability curve: age 85 years, index case.

Appendix 16

Parameters for estimation of the distributions for the probabilistic model (base case)

TABLE 73 Cost parameters

Parameter	Value	Low	High	Source	Distribution	Alpha	Beta
Costs of cardiovascular events (£)							
No event	74			NICE 2008[1]	Gamma	25	2.96
MI (first year)	3780			NICE 2008[1]	Gamma	25	151.1952
MI (subsequent)	500			NICE 2008[1]	Gamma	25	20
Stroke (first year)	4335			NICE 2008[1]	Gamma	25	173.4137
Stroke (subsequent)	2336			NICE 2008[1]	Gamma	25	93.44554
PAD (first year)	2212			NICE 2008[1]	Gamma	25	88.4974
PAD (subsequent)	285			NICE 2008[1]	Gamma	25	11.4053
Heart failure (first year)	4379			NICE 2008[1]	Gamma	25	175.1699
Heart failure (subsequent)	500			NICE 2008[1]	Gamma	25	20
Revascularisation (first year)	8610			NICE 2008[1]	Gamma	25	344.3940
Revascularisation (subsequent)	500			NICE 2008[1]	Gamma	25	20
Unstable angina (first year)	2074			NICE 2008[1]	Gamma	25	82.9677
Unstable angina (subsequent)	500			NICE 2008[1]	Gamma	25	20
Additional cost parameters							
Cost per MOLU	30	20	40	Personal communication	Beta	1	1
Cost LDL-C	19.97	15.97	23.96	Assumed high and low	Beta	1	1
Cost low-intensity statins	17.21	13.77	20.65	Assumed high and low	Beta	1	1
Cost high-intensity statins	377	302	453	Assumed standard error	Gamma	25	15.0993
Test sensitivity and specificity							
Elucigene sensitivity	0.4397	0.286[a]	0.52[a]	Taylor 2010[37]	Beta	102	130
LIPOchip sensitivity	0.7846	0.33[a]	0.945[a]	Palacios 2010[41]	Beta	57	8
LIPOchip platform – Spain, sensitivity	0.8776	0.805	1	Assumption	Beta	57	8
LDL-C index cases, sensitivity	0.9	0.72	1	Damgaard, 2005[45]	Beta	1	1
LDL-C (relatives) sensitivity	0.576	0.469	0.679	Starr, 2008[49]	Beta	50.36	37.07
LDL-C (relatives) specificity	0.837	0.8	0.87	Starr, 2008[49]	Beta	401.99	78.29
Health-state multipliers							
MI	0.76	0.56	0.96	NICE 2008[1]	Beta	427.09	134.8711
Post MI	0.88	0.78	1.00	NICE 2008[1]	Beta	285.93	38.9911
Stroke	0.629	0.43	0.83	NICE 2008[1]	Beta	91.1103	53.7391
Post stroke	0.629	0.43	0.83	NICE 2008[1]	Beta	91.1103	53.7391
PAD	0.9	0.86	0.98	NICE 2008[1]	Beta	201.6	22.4

continued

TABLE 73 Cost parameters (*continued*)

Parameter	Value	Low	High	Source	Distribution	Alpha	Beta
Post PAD	0.9	0.86	0.98	NICE 2008[1]	Beta	201.6	22.4
Heart failure	0.683	0.48	0.88	NICE 2008[1]	Beta	369.0095	171.268
Post heart failure	0.683	0.48	0.88	NICE 2008[1]	Beta	369.0095	171.268
Revascularisation	0.93	0.74	1.00	NICE 2008[1]	Beta	31.3118	2.3568
Post revascularisation	0.93	0.74	1.00	NICE 2008[1]	Beta	40.9973	3.0858
Unstable angina	0.77	0.57	0.97	NICE 2008[1]	Beta	420.1158	125.4891
Post unstable angina	0.88	0.78	1.00	NICE 2008[1]	Beta	285.9348	38.9911
General population quality of life							
< 25 years	0.94	0.705	1	NICE 2008[1]	Beta	1	1
25–34 years	0.93	0.636	1	NICE 2008[1]	Beta	1	1
35–44 years	0.91	0.596	1	NICE 2008[1]	Beta	1	1
45–54 years	0.85	0.36	1	NICE 2008[1]	Beta	1	1
55–64 years	0.8	0.29	1	NICE 2008[1]	Beta	1	1
65–74 years	0.78	0.27	1	NICE 2008[1]	Beta	1	1
75+ years	0.73	0.20	1	NICE 2008[1]	Beta	1	1
Treatment effect for each health state in the model							
MI	0.81	0.72	0.91	Assumed standard error	Beta	47.079	11.0432
Stroke	0.82	0.70	0.96	Assumed standard error	Beta	22.902	5.0273
TIA	0.79	0.65	0.94	Assumed standard error	Beta	21.587	5.7383
PAD	0.87	0.69	1.00	Assumed standard error	Beta	21.497	3.2122
Heart failure	0.77	0.65	0.92	Assumed standard error	Beta	22.513	6.7247
Revascularisation	0.78	0.69	1.00	Assumed standard error	Beta	9.8438	2.7764
Unstable angina	0.84	0.71	0.86	Assumed standard error	Beta	1083.4132	206.3644
CVD death	0.92	0.72	1.00	Assumed standard error	Beta	39.7241	3.4543
Death other	1.00	0.80	1.00	Assumed standard error	Beta	1	1

CVD, cardiovascular disease; PAD, peripheral arterial disease; TIA, transient ischaemic attack.
a Bounded between high and low values of all reported studies for that test.

Appendix 17

Cost-effectiveness acceptability curves for alternative mutation test-positive rates on comprehensive genetic analysis

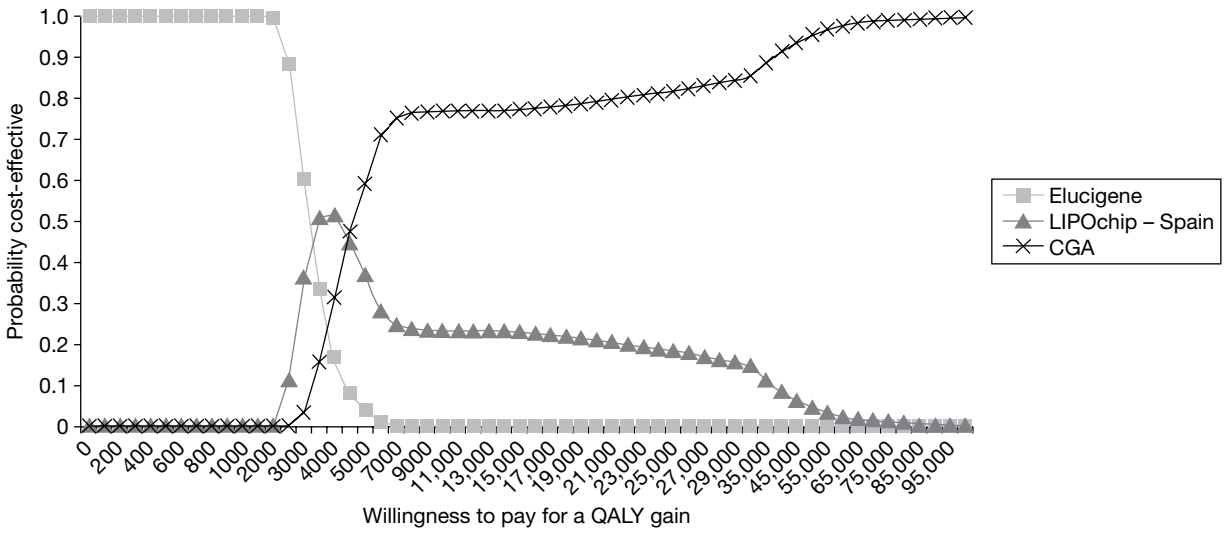

FIGURE 18 Cost-effectiveness acceptability curve: incidence of genetic mutation = 5%.

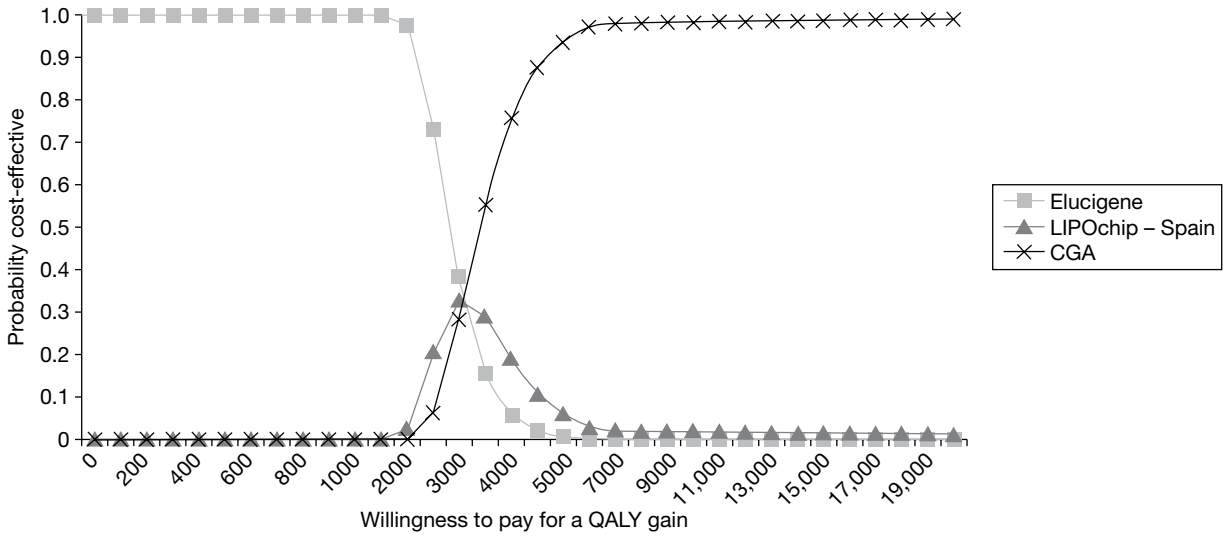

FIGURE 19 Cost-effectiveness acceptability curve: incidence of genetic mutation = 10%.

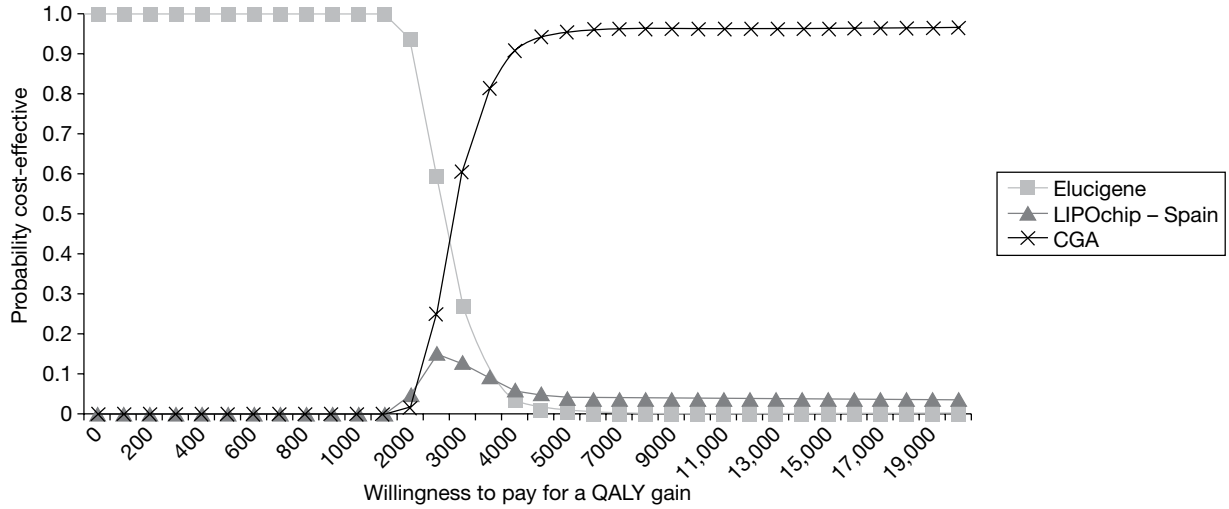

FIGURE 20 Cost-effectiveness acceptability curve: incidence of genetic mutation = 20%.

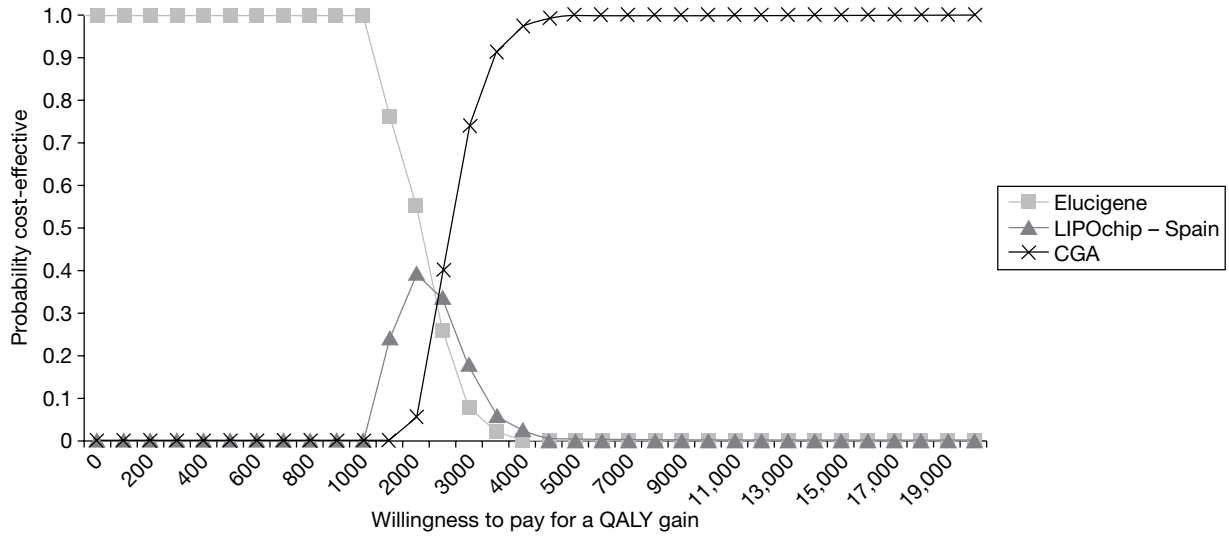

FIGURE 21 Cost-effectiveness acceptability curve: incidence of genetic mutation = 50%.

Appendix 18

Proportion identified by cascade testing using comprehensive genetic analysis (targeted sequencing) or age- and gender- specific low-density lipoprotein cholesterol cut-offs

Study	Country	Clinical diagnosis of index cases	Study participants	Number of participants	Test for cascading	Proportion identified from cascade testing
Bourbon 2008[85]	Portugal	Simon Broome criteria	Relatives of index cases	Index cases = 88; relatives = 206 Families = 165; relatives = 226	Targeted sequencing (*LDLR*/*APOB*/*PCSK9*). Index cases tested with dHPLC/ sequencing/MLPA	56% (116/206) (as of 2008); 51% (226/443) (as of 2010)
Hadfield 2009[66]	UK	Definite or possible Simon Broome criteria	First-degree relatives of index cases	Index cases = 931; relatives = 591	LDL-C age- and gender-specific cut-offs according to NICE guideline. Living in catchment area	Likely plus uncertain = 42% (250/591); likely = 28% (168/591); uncertain = 14% (82/591)
				Relatives = 178	LDL-C age- and gender-specific cut-offs according to NICE guideline. Living in non-catchment area	Likely plus uncertain = 40% (72/178); likely = 29% (51/178); uncertain = 12% (21/178)
Humphries 2006[84]	UK	Definite or possible Simon Broome criteria	First-degree relatives of index cases	Index cases = 69; relatives = 54	Targeted sequencing (*LDLR*/*APOB*). Index cases tested with SSCP/ sequencing/ UPQFM-PCR	50% (27/54)
Leren 2008[11]	Norway	Not reported	First-degree relatives of index cases	Index cases = 440; relatives = 1805	Targeted sequencing (*LDLR*/*APOB*). Index cases tested with sequencing/ MLPA/PCR for *APOB*	45% (808/1805)
Umans-Eckenhausen 2001[19]	The Netherlands	Dutch criteria	First- and second-degree relatives of index cases	237 families; relatives = 2039	Targeted sequencing (*LDLR*/*APOB*). Index cases tested with DGGE/ sequencing/ restriction digest analysis	37% (2039/5442)
Vergotine 2001[83]	South Africa		Families of index cases	Index cases = 379; relatives = 790	Targeted sequencing (*LDLR*)	43% (338/790)

UPQFM-PCR, universal primer quantitative fluorescent multiplex PCR.

Appendix 19

Protocol

Final protocol, 16th December 2010

1. Title of the project

The clinical and cost-effectiveness of Elucigene FH20 and LIPOchip for the diagnosis of familial hypercholesterolaemia: systematic review and economic evaluation.

2. Name of External Assessment Group (EAG) and project lead

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3. Plain English Summary

Familial hypercholesterolaemia (FH) is an inherited (genetic) condition resulting in raised levels of cholesterol in the blood. A person can either inherit the genetic defect from one parent (heterozygous FH) or from both parents (homozygous FH). In the UK heterozygous FH has a frequency of 1 in 500, affecting around 100,000 people in England, while homozygous FH is

much rarer, with a frequency of 1 in one million.[1] The condition is transmitted from generation to generation, so that the siblings or children of a person with FH have a 50% risk of inheriting the genetic defect.

The raised levels of cholesterol in the blood that characterise heterozygous FH lead to a greater than 50% risk of coronary heart disease (CHD) by the age of 50 in men and at least 30% risk in women by the age of 60.[2] If untreated, around 50% of men will die before the age of 60.[3] People with homozygous FH have a significantly poorer prognosis than those with heterozygous FH.

FH is generally characterised by the presence of increased levels of cholesterol concentration and clinical symptoms such as tendon xanthomata (yellowish skin lesions on the tendons of the hands and feet) and a family history of CHD. However there are variations in the time at which clinical signs and CHD appear.[4] Tendon xanthomata, which are frequent but not always present, may be seen in the second decade of life, while CHD is usually present by the fourth decade. Diagnosis of FH by cholesterol concentration is not entirely reliable[3] with a 10% risk of misdiagnosis.[5] FH is an underdiagnosed condition, with at least 75% of people in the UK with heterozygous FH remaining undiagnosed.[6]

The NICE clinical guideline on identification and management of familial hypercholesterolaemia recommends that a diagnosis of FH should be made using the Simon Broome criteria, which include a combination of family history, clinical signs, cholesterol concentration and DNA testing, to improve diagnosis and early identification of FH.[7] Cascade testing (a mechanism for identifying people at risk of FH by a process of family tracing) using a combination of DNA testing and low density lipoprotein cholesterol (LDL-C) concentration measurement is recommended to identify affected relatives of those individuals with a clinical diagnosis of FH.[7] The aim of early identification is to reduce the risk of vascular diseases by starting treatment with cholesterol-lowering drugs such as statins and by allowing management by lifestyle changes and diet modification.[8] The use of statins, even in lower doses than recommended, can reduce the risk of CHD in patients with FH.[9] The standard method of DNA testing is comprehensive genetic analysis, which is the most complete genetic analysis generally available for FH within a diagnostic setting; however the process is slow and expensive (estimated at around £500 to £1000 per patient in the UK setting).[10,11] Elucigene FH20[12] and LIPOchip[13] are recently developed rapid genetic testing kits that are designed to detect a more limited number of genetic mutations associated with FH that are commonly found in the UK population.

This systematic review will assess the clinical and cost-effectiveness of the Elucigene FH20 kit, LIPOchip, and comparators, for the diagnosis and cascade testing of FH.

4. Decision problem

4.1 Purpose of the decision to be made

The purpose of this appraisal is to address the following questions:

1. What are the most effective and cost-effective strategies for confirming a diagnosis of FH in index individuals and for cascade testing of relatives?
2. In cascade testing of relatives for mutations identified in index individuals by Elucigene FH20 or LIPOchip, would it be more cost-effective to use those tests rather than targeted gene sequencing?

4.2 Clear definition of the intervention

Elucigene FH20

The Elucigene FH20 kit (Gen-Probe Life Sciences, UK), using the principle of an amplification refractory mutation system (ARMS), is designed to detect 20 genetic mutations associated with FH that are commonly found in the UK population (see Table 1).[14] These mutations, with a frequency ranging from 1.3% to 11.4%, were identified from a cohort study involving 400 patients in the UK with FH.[15] Of the 20 mutations, 18 are found in the Low-density lipoprotein receptor (LDLR) gene, one in the Apolipoprotein B (APOB) gene and one in the Protein convertase subtilisin/kexin 9 (PCSK) gene (Table 1).[14]

By using ARMS, the Elucigene FH20 kit combines the amplification step and diagnostic steps,[16] making the process faster. A limitation of the kit is that it only tests for 20 FH mutations. Worldwide approximately 1200 FH-causing mutations have been identified,[17] of which over 200 have been reported in the UK population.

LIPOchip

LIPOchip (Progenika Biopharma, Spain) is an alternative genetic test designed to diagnose FH.[13] LIPOchip is a tiered system that uses DNA array technology. The chip can detect point mutations, copy number changes and variation of number of copies of the LDLR gene. The current version (version 10) tests for 189 mutations in the LDLR, APOB and PCSK genes that are known to occur in the UK population.

The LIPOchip platform involves the following steps:

(a) Firstly, samples are analysed using the DNA array which is designed to detect 189 mutations in the LDLR and APOB genes.
(b) If the samples fail to detect these mutations they are analysed for large gene re-arrangements.
(c) If the first two steps fail to detect mutations then samples are analysed by automated sequencing of the LDLR.
(d) If all three of the above steps fail to detect mutations then the sample is confirmed as FH negative.
(e) Finally, the LIPOchip software generates a report containing information on the pathogenicity of detected mutations.

The manufacturer also offers a LIPOchip test processing service from its laboratory in Spain.

4.3 Populations and relevant subgroups

The populations considered are adults and children with a clinical diagnosis of FH (the index individuals/probands) based on the Simon Broome criteria, and, for cascade testing, first-, second- and third-degree biological relatives.

TABLE 1 FH genetic mutations detected by Elucigene FH20

Gene	Mutation
Low-density lipoprotein receptor (LDLR)	P664L, L458P, R329X, E207X, D200G, E80K, IVS3+1G>A, D461H, ΔG197, fs206, Q363X, W66G, V408M, D206E, C656R, K290RfsX20, C163Y and D461N
Apolipoprotein B (APOB)	R3500Q
Protein convertase subtilisin/kexin 9 (PCSK9)	D374Y

4.4 Place of the interventions in the treatment pathway(s)

The care pathway for this assessment is based on the NICE clinical guideline on the identification and management of FH.[7]-

Index individuals

The assessment will investigate the effect of diagnostic strategies including Elucigene FH20 and/or LIPOchip for providing an unequivocal diagnosis of FH for those with a clinical diagnosis based on the Simon Broome criteria.

Cascade testing of relatives

The assessment will investigate the effect of diagnostic strategies including Elucigene FH20 for cascade testing to identify FH in the relatives of index individuals. The use of Elucigene FH20 for cascade testing will depend on the mutation detected in the index individual and the cost of targeted gene sequencing. (In index individuals with an identified genetic mutation, depending on the test used to detect the mutation, targeted gene sequencing will also be considered for cascade testing of relatives. In index individuals without an identified genetic mutation, cascade testing using LDL-C concentration measurement will be considered.)

A scenario encompassing a single test strategy (Elucigene FH20 or LIPOchip) that does not end in comprehensive genetic analysis for test negatives may not detect all cases of FH. In such a scenario there may be implications for test negative patients in terms of how their condition is managed.

4.5 Relevant comparators

Comprehensive genetic analysis

Comprehensive genetic analysis is defined as the most complete genetic analysis generally available for FH within a diagnostic setting and is expected to detect almost all known FH causing mutations. This analysis will include DNA sequence analysis of the promoter, all exons, the exon/intron boundaries and into 3′ untranslated region of the LDLR gene that will detect the majority (~88%) of detectable FH mutations, multiplex ligation-dependent probe amplification (MLPA)[18] for each exon and the promoter region of the LDLR gene to detect deletions and duplications (~5% detectable FH mutations) plus analysis for the common APOB p.Arg3527Gin gene mutation (~5% FH mutations) and the PCSK9 p.Asp374Tyr gene mutation (~2% FH mutations).

Multiplex ligation-dependent probe amplification (MLPA) (MRC-Holland) is a commercial kit that enhances the molecular diagnosis of FH with an ability to detect large deletions and or duplications for each of the LDLR 18 exons.[18] Comprehensive genetic analysis including DNA sequencing with MLPA is considered to be the 'gold standard' of genetic testing.

Targeted gene sequencing

Targeted gene sequencing (the genetic test for sequencing a specific part of the gene where a family mutation is found) may be used for cascade testing to identify FH in the relatives of index individuals. The use of targeted sequencing for cascade testing will depend on the test used to detect a genetic mutation in the index individual.

LDL-C concentration as part of the Simon Broome criteria

In UK a clinical diagnosis of FH should be made based on the Simon Broome criteria,[7] which include a combination of family history of CHD, clinical signs such as tendon xanthomata, cholesterol concentration and DNA testing[11,19] (*Table 2*). This approach categorises FH as 'definite' or 'possible'. DNA based evidence was subsequently introduced into the criteria for provision of

TABLE 2 Simon Broome diagnostic criteria[11,19]

Criteria required for clinical diagnosis of FH	Definite FH	Possible FH
Cholesterol concentration: Child/young person: Total cholesterol (TC) > 6.7 mmol/L, Low density lipoprotein cholesterol (LDL-C) > 4 mmol/L; Adult: TC > 7.5 mmol/L, LDL-C: > 4.9 mmol/L	Yes	Yes
Clinical symptoms: Tendon xanthomata, or evidence of these signs in first- or second-degree relative	Yes	No
Family history of: ■ myocardial infarction in second degree relative (aged < 50 years) or in first degree relative (aged < 60 years), or ■ raised TC (> 7.5 mmol/L in adult first, second degree relative, or > 6.7 mmol/L in child and sibling < 16 years)	No	Yes (at least one of these criteria)

Or DNA based evidence of mutation in LDL-R, APOB or PCSK9 genes gives an unequivocal diagnosis of FH.

an unequivocal diagnosis of FH. However, around 10% of people with FH do not meet the Simon Broome criteria.

LDL-C concentration is usually estimated from a fasting blood sample using the Friedwald equation. Due to NHS commissioning arrangements of genetic tests, LDL-C concentration measurement is the main test currently used to diagnosis FH in index cases and for cascade testing of relatives.[20] However, it has some limitations in terms of diagnostic accuracy, including:

1. There is an overlap in LDL-C levels between affected and unaffected individuals, and the cut-offs used can result in diagnostic ambiguity in an estimated 15% of children (aged 5–15 years) and in nearly 50% of adults (aged 45–55 years).[21,22]
2. In children who are at risk of FH, cholesterol levels may appear normal initially with the levels rising only later in life.[23]
3. Girls generally have lower cholesterol concentration than boys at an early age but may go on to develop CHD in later years.[22]

Age adjusted LDL-C measurement has been found to give better clinical diagnosis of FH, with a sensitivity of 72% and specificity of 71%.[24] The gender- and age-specific LDL-C criteria rather than the Simon Broome LDL-C criteria are the recommended criteria for cascade testing of relatives of index individuals.[7]

4.6 Key factors to be addressed

This systematic review will aim to:

1. Assess the diagnostic accuracy and clinical effectiveness of Elucigene FH20, LIPOchip and comparators in confirming a diagnosis of FH in patients with a clinical diagnosis of FH.
2. Assess the diagnostic accuracy and clinical effectiveness of Elucigene FH20 and comparators in cascade testing of relatives of index individuals with a confirmed diagnosis of FH.
3. Estimate the costs of different diagnostic strategies for detecting FH in index individuals and for cascade testing of relatives of index individuals with a confirmed diagnosis of FH.

5. Report methods for assessing the outcomes arising from the use of the interventions

A systematic review of the evidence on Elucigene FH20 and LIPOchip for the diagnosis of familial hypercholesterolaemia will be undertaken following the general principles of the Centre for Reviews and Dissemination (CRD) guidance for conducting reviews in health care[25] and NICE Diagnostics Assessment Programme interim methods statement.[26]

5.1 Inclusion and Exclusion criteria

Population

The populations considered are adults and children with a clinical diagnosis of FH (the index cases/probands) based on the Simon Broome criteria, and, for cascade testing, first-, second- and third-degree biological relatives of the index individual.

If the evidence allows, subgroup analysis will be undertaken on the performance of Elucigene FH20 and LIPOchip in ethnic populations.

Setting

The setting considered is secondary or tertiary care.

Interventions

The interventions considered are Elucigene FH20 and LIPOchip for index cases and Elucigene FH20 for cascade testing.

Comparators

The comparators for testing in index individuals are (i) comprehensive genetic analysis and (ii) LDL-C concentration measurement (Simon Broome criteria). The comparators for cascade testing of relatives are (i) targeted gene sequencing and (ii) LDL-C concentration measurement (gender- and age-specific criteria as recommended in NICE CG71).

Reference standard

The reference standard is comprehensive genetic analysis in combination with the Simon Broome Criteria.

Outcomes

The following outcomes will be considered:

(a) Test accuracy;
(b) Mutation detection rate – proportion of cases with an unequivocal diagnosis identified by Elucigene and LIPOchip;
(c) Proportion requiring comprehensive genetic analysis after Elucigene and LIPOchip; and
(d) Proportion of FH identified from cascade testing;

In any studies reporting the above outcomes the following outcomes will also be considered if reported:

(a) Acceptability of the tests; and
(b) Interpretability of the tests.

Studies reporting test accuracy must report the absolute numbers of true positives, false positives, false negatives and true negatives, or provide information allowing their calculation.

Study design

The following types of studies will be included:

(a) Direct (head-to-head) studies in which the index test, comparator test and reference standard test are done independently in the same group of people.
(b) Randomised controlled trials (RCTs) in which people are randomised to the index and comparator test(s) and all receive the reference standard test.

In case of insufficient evidence from direct and randomised studies, we will consider indirect (between-study) comparisons of the following types of study:

(a) Diagnostic cross-sectional studies comparing the index test or comparator test against a reference standard test.
(b) Case–control studies in which two groups are created, one known to have the target disease and one known not to have the target disease, where it is reasonable for all included to go through the tests.

Exclusion criteria

We will exclude the following types of report:

- Preclinical and biological studies
- Reviews, editorials and opinions
- Case reports
- Reports investigating technical aspects of a test

Non-English language reports may be excluded if the evidence base containing English-language reports is sufficiently large.

5.2 Search strategy

Extensive electronic searches will be conducted to identify reports of published and ongoing studies on Elucigene FH20 and LIPOchip for the detection and cascade testing of FH. The search strategies will be designed to retrieve all studies that assess the diagnostic accuracy and clinical effectiveness of the index, comparator and reference standard tests. Searches will be restricted to publications from 2000 onwards. Both full-text papers and recent conference abstracts will be sought. Potentially relevant non-English-language studies will be excluded and listed in an appendix to the review, unless the English-language evidence base is deemed to be insufficient in which case they will be included. Databases to be searched will include: MEDLINE, EMBASE, Science Citation Index, Biosis and the Cochrane Controlled Trials Register. A preliminary MEDLINE search strategy is shown in Appendix A and will be adapted for use in other databases.

A search for systematic reviews and other background publications will also be undertaken. Sources will include the Cochrane Database of Systematic Reviews, HTA Database and DARE.

Current research registers, including Current Controlled Trials, Clinical Trials and WHO International Clinical Trials Registry will be searched. Recent conference proceedings of key organisations will also be screened and will include the European Society of Human Genetics, American Association for Clinical Chemistry, International Atherosclerosis Society and Heart UK.

In addition, an internet search using Copernic Agent will be undertaken and will also include key professional organisations.

5.3 Data extraction strategy

Two reviewers will independently screen the titles (and abstracts if available) of all reports identified by the search strategy. Full-text copies of all studies deemed to be potentially relevant will be obtained, and two reviewers will independently assess them for inclusion. Any disagreements will be resolved by consensus or arbitration by a third party.

A data extraction form will be developed and piloted. One reviewer will extract details of study design, participants, index, comparator, reference standard tests and outcome data. A second reviewer will check the data extraction. Any disagreements will be resolved by consensus or arbitration by a third party.

Study data requested and received from the manufacturers that meet the inclusion criteria, and are received in time to be incorporated into the review, will be extracted and quality assessed in accordance with the procedures outlined in this protocol.

5.4 Quality assessment strategy

Two reviewers will independently assess the methodological quality of the included diagnostic studies. Any disagreements will be resolved by consensus or arbitration by a third party. Studies will not be included or excluded on the basis of methodological quality.

Various quality assessment tools will be used depending upon the type of studies included. For instance, included diagnostic studies will be quality assessed using QUADAS, a quality assessment tool developed for use in systematic reviews of diagnostic studies.[27] The quality assessment tool will be adapted to make it more applicable to assess the quality of studies of tests for detecting FH.

5.5 Methods of analysis/synthesis

Analysis will focus on the ability of Elucigene FH20, LIPOchip and relevant comparators to detect FH. Where appropriate two by two tables will be extracted from each included study where information is provided on the numbers of true and false-positives and negatives for the index and/or comparator test compared with the reference standard for detecting those mutations that the index and/or comparator test are designed to identify. For each study we will attempt to calculate sensitivity, specificity, positive and negative likelihood ratios and diagnostic odds ratios and their confidence intervals.

Where appropriate and given sufficient information, we will use summary receiver operating characteristic (SROC) curves for the meta-analysis of data from studies reporting estimates of true and false-positives and negatives. This approach characterises the relationship between sensitivity and 1–specificity across studies and takes into account variation in the threshold for test positivity between studies. ROC curves will be generated, where possible, for each testing procedure. Where data are available, potential sources of heterogeneity will be investigated by extending the SROC regression models to include study level covariates. These potential sources of heterogeneity include characteristics of the population such as age, race, family history and whether the test is cascade testing.

Where appropriate, models will be fitted using the hierarchical summary receiver operating characteristic (HSROC) framework, which takes proper account of the diseased and non-diseased sample sizes in each study, and allows estimation of random effects for the threshold and accuracy effects, and testing of the impact of potential sources of heterogeneity. Estimates and their CI's for the average operating points, expressed as sensitivity, specificity and likelihood ratios will be obtained by combining these estimates.[28]

Average and ranges of feasible operating points will be identified on the fitted ROC points to convert ROC curve values into estimates of true positive and false positive rates which will serve as parameters within the economic model.

5.6 Methods for estimating quality of life – relevance to the decision analysis

Quality of life estimates used in the economic model will be informed by the current NICE guideline on the identification and management of familial hypercholesterolaemia[7] and relevant literature searches together with clinical expert opinion as appropriate. As FH is a chronic disease requiring long-term care, we will extrapolate cost and QALY values over a life-time horizon and discount both cost and QALYs at a rate of 3.5% as recommended by NICE. This will use a linked evidence approach linking diagnostic accuracy of the various strategies with any potential changes in clinical management and thus life-time final health outcomes. The economic model informing current NICE guideline CG71 for treatment of FH will be validated and used to estimate the final treatment outcomes.

6. Report methods for synthesising evidence of cost-effectiveness

A systematic search for existing cost-effectiveness literature will be undertaken for diagnostic assessment strategies for the detection of genetic mutations causing familial hypercholesterolaemia.

6.1 Identifying and systematically searching published cost-effectiveness studies.

Studies will be sought, reporting both costs and outcomes for diagnostic assessment strategies, from a systematic review of the literature. No language restrictions or limitations to searches will be imposed.

Databases to be searched will include MEDLINE, EMBASE, Science Citation Index, NHS EED, HTA Database, Health Management Information Consortium and the CEA Registry. In addition, reference lists of all included studies will be scanned to identify additional potentially relevant studies. A draft MEDLINE search strategy is appended and will be adapted for use in the other databases.

6.2 Evaluation of costs and cost-effectiveness

The evidence on costs and cost-effectiveness will be evaluated using the NICE Diagnostics Assessment Programme interim methods.[26] An economic model will be developed to estimate the cost-effectiveness of each care pathway and link this to final treatment outcomes. Current NICE guideline CG71 will be used to inform the development of this approach.

6.3 Development of a health economic model

An economic evaluation of the cost-effectiveness of Elucigene, LIPOchip and identified comparators will be conducted. An economic model will be developed to determine which diagnostic and treatment strategy is the most cost-effective use of scarce NHS resources for genetic testing for FH among proband cases (identified using the Simon Broome criteria) and cascade testing of relatives.

The primary economic model output will be incremental cost per quality adjusted life year (QALY) gained associated with the use of a variety of genetic testing strategies for the detection of FH. A life-time horizon will be used in the model and costs and benefits will be discounted at a rate of 3.5% as recommended by NICE.[29] The development of this economic model will be an iterative approach and it will be developed in a way that is adaptable to the analysis of new and

emerging technologies. A possible scenario for the modelling is presented in Appendix B for the index cases and Appendix C for the cascade testing of their relatives (Appendix B, Appendix C). A range of diagnostic strategies will be explored initially for index patients with a clinical diagnosis based on the Simon Broome criteria. The model will further estimate the most cost-effective method of cascade testing for FH in first-, second-, and possibly third-degree relatives of the index patient. This too will be presented as incremental cost per QALY gained. We note that the diagnostic test used to detect the family mutation may not be the same as that used to detect the mutation in the index individual. This is due to the potential for cost savings among alternative cheaper tests for cascade testing (e.g. Elucigene) once the FH-causing family mutation has been identified. Our analysis will be from the perspective of the NHS as well as a personal social services perspective as appropriate. Any assumptions made in the modelling approach and parameter development will be taken primarily from the literature and supplemented by clinical expert opinion as appropriate/required.

Health related quality of life and QALY data for lifelong health outcomes have already been modelled in terms of management of FH in cascade testing and treatment strategy. These data will be validated, updated as necessary and used to help populate the economic model being developed. Any evidence on detection rates and diagnostic accuracy of the comparators will be sourced from the literature. As it is unlikely that a large evidence base exists in the literature, data will be supplemented by clinical expert opinion as required. A key challenge in terms of diagnostic accuracy of the genetic testing kits will be to generalise detection rates to the general UK population. It is likely that detection rates will vary depending on ethnicity and so this will need to be fully understood and uncertainties explored through sensitivity analyses. Data from the genetic bank held in London, together with manufacturer and clinical expert supplied input will be used to estimate detection rates of the different strategies.

Resource use and costs for detection are likely to be the major driver of the cost-effectiveness results. It will be important to fully incorporate all economic costs associated with testing and processing diagnostic samples for each treatment strategy and the range of scenarios required by the model. A combination of national resources such as NHS reference costs, the Personal Social Services Research Unit (PSSRU) and the British National Formulary (BNF) will be used as appropriate together with any other relevant sources of data identified. Costs of diagnostic kits will be sourced from the manufacturers and costs of processing samples sourced from a combination of manufacturer and clinical expert data. As obtaining test results is not time sensitive due to the clinical nature of FH, the base case analysis will assume genetic laboratories will batch test to gain maximum efficiency (i.e. minimum cost). The impact of operating testing procedures below maximum efficiency will be considered in model sensitivity analyses. A key challenge will be to generalise the cost of comprehensive genetic analysis across the UK, where various laboratories report different unit workload costs. The effect of alternative costing strategies will be explored through model sensitivity analyses.

The development of this economic model will be an iterative approach. As the evidence base changes and new evidence arises, the economic model structure and parameters will evolve to reflect this. We further suspect that the evidence base will be lacking for some of the model parameters. With this in mind, uncertainty in model parameters will be explored in terms of their outputs through a range of one-way and multi-way sensitivity analyses deemed appropriate as the modelling progresses. As we anticipate a lack of evidence to inform the model, we will explore parameter uncertainty through probabilistic sensitivity analyses, with the generation of cost-effectiveness acceptability curves illustrating this uncertainty graphically.

7. Handling information from the companies

Following a request for information, any 'commercial in confidence' data provided by a manufacturer and specified as such will be highlighted in blue and underlined in the assessment report (followed by an indication of the relevant company name e.g. in brackets).

8. Competing interests of authors

None

9. Timetable/milestones

Milestones	Date to be completed
Draft protocol	24/11/10
Final protocol	14/12/10
Progress report	w/c 18/02/11
Draft version of report	01/04/11
Final version of report	28/04/11

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11. Appendices

Appendix A

Preliminary MEDLINE strategy

Diagnostic Accuracy and Clinical Effectiveness of Elucigene FH20, LIPOchip and Comparators

1. Hyperlipoproteinemia Type II/di [Diagnosis]
2. lipochip.tw.
3. elucigene.tw.
4. Hyperlipoproteinemia Type II/
5. hyperlipidemia, familial combined/
6. familial hypercholesterol?emia.tw.
7. hyperlipoprotein?emia.tw.
8. familial hyperlipid?emia.tw.
9. or/4-8
10. exp Genetic Predisposition to Disease/
11. Genetic Testing/
12. Gene Amplification/
13. exp Nucleic Acid Amplification Techniques/
14. exp oligonucleotide array sequence analysis/ or exp sequence analysis, dna/
15. (dna adj3 test$).tw.
16. gene sequencing.tw.
17. (sequenc$ adj3 analysis).tw.
18. (cascade adj3 (test$ or screen$)).tw.
19. (genetic adj3 (test$ or screen$)).tw.
20. (arms or amplification refractory mutation system).tw.
21. (PCR or polymerase chain reaction).tw.
22. Polymorphism, Single-Stranded Conformational/
23. (sscp or single-stranded conformation polymorphism).tw.
24. (mlpa or Multiplex ligation-dependent probe amplification).tw.
25. Cholesterol, LDL/
26. ldl-c.tw.
27. or/10-26
28. 9 and 27
29. "sensitivity and specificity"/
30. roc curve/
31. predictive value of tests/

32. false positive reactions/
33. false negative reactions/
34. du.fs.
35. sensitivity.tw.
36. distinguish$.tw.
37. differentiat$.tw.
38. identif$.tw.
39. detect$.tw.
40. diagnos$.tw.
41. (predictive adj4 value$).tw.
42. accura$.tw.
43. comparison.tw.
44. or/29-43
45. 28 and 44
46. 1 or 2 or 3 or 45
47. limit 46 to yr=”2000 -Current»
48. randomized controlled trial.pt.
49. controlled clinical trial.pt.
50. randomi?ed.ab.
51. placebo.ab.
52. drug therapy.fs.
53. randomly.ab.
54. trial.ab.
55. groups.ab.
56. or/48-55
57. exp animals/ not humans/
58. 56 not 57
59. 28 and 58
60. limit 59 to yr=”2000 -Current»
61. 46 or 60

Preliminary MEDLINE strategy

Economic evaluations of Elucigene FH20, LIPOchip and Comparators

1. Hyperlipoproteinemia Type II/di
2. elucigene.tw
3. lipochip.tw
4. Hyperlipoproteinemia Type II/
5. hyperlipidemia, familial combined/
6. familial hypercholesterol?emia.tw.
7. hyperlipoprotein?emia.tw.
8. familial hyperlipid?emia.tw.
9. or/4-8
10. genetic predisposition to disease/
11. genetic testing/
12. (genetic adj3 (test$ or screen$)).tw.
13. (cascade adj3 (test$ or screen$)).tw.
14. (dna adj3 test$).tw
15. gene amplification/
16. exp Nucleic Acid Amplification Techniques/
17. exp sequence analysis,dna/
18. exp oligonucleotide array sequence analysis/

19. (arms or amplification refractory mutation system).tw.
20. (PCR or polymerase chain reaction).tw
21. (sscp or single-stranded conformation polymorphism).tw
22. (mlpa or Multiplex ligation-dependent probe amplification).tw.
23. gene sequencing.tw.
24. sequence analys?s.tw.
25. ldl-c.tw.
26. or/10-25
27. 9 and 26
28. or/1-3,27
29. exp "costs and cost analysis»/
30. economics/
31. exp economics,medical/
32. economics,pharmaceutical/
33. exp budgets/
34. exp models, economic/
35. exp decision theory/
36. monte carlo method/
37. markov chains/
38. exp technology assessment, biomedical/
39. cost$.ti.
40. (cost$ adj2 (effective$ or utilit$ or benefit$ or minimis$)).ab.
41. economics model$.tw.
42. economic$ .tw.
43. (price or prices or pricing).tw.
44. (value adj1 money).tw.
45. markov$.tw.
46. monte carlo.tw.
47. (decision$ adj2 (tree? or analy$ or model$)).tw.
48. or/29-47
49. 28 and 48

Appendix B

Patient care pathways (Index cases with a clinical diagnosis of FH using the Simon Broome criteria – including a LDL-c test)*

*The above is a guideline to the main strategies, there may be exceptions to these strategies which will be explored as the analysis progresses.

1.	Elucigene	→	Treatment decision				
2.	Elucigene	→	Lipochip for negatives	→	Treatment decision		
3.	Elucigene	→	MLPA for negatives	→	Treatment decision		
4.	Elucigene	→	CGA for negatives	→	Treatment decision		
5.	Elucigene	→	Lipochip for negatives	→	GA for negatives	→	Treatment decision
6.	Elucigene	→	Lipochip for negatives	→	MLPA for negatives	→	Treatment decision
7.	Lipochip	→	Treatment decision				
8.	Lipochip	→	CGA for negatives	→	Treatment decision		
9.	Lipochip	→	MLPA for negatives	→	Treatment decision		
10.	CGA	→	Treatment decision				
11.	LDL-c	→	Treatment decision (current practice)				

Appendix C

Patient care pathways (Cascade testing of relatives of FH identified index patients)**

**Once a relative is found to be negative for the mutation being tested for, cascade testing stops and further cascade testing is not conducted

Index case identified by	Cascade testing of relatives		Clinical management
Elucigene	Elucigene	→	Treatment decision
Elucigene	Targeted Sequencing	→	Treatment decision
Lipochip	Elucigene	→	Treatment decision
Lipochip	Targeted Sequencing	→	Treatment decision
CGA	Elucigene	→	Treatment decision
CGA	Targeted Sequencing	→	Treatment decision

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Feedback

The HTA programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

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