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

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Executive summary

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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.

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NIHR Health Technology Assessment programme

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