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


CRD summary
This review assessed Elucigene FH20 and LIPOchip for diagnosis of familial hypercholesterolaemia and concluded that neither can detect all cases of familial hypercholesterolaemia. Comprehensive genetic analysis remained the most cost-effective method of confirming a clinical diagnosis and testing relatives of an affected person. This conclusion is likely to be reliable.

Authors' objectives
To assess the diagnostic accuracy, effect on patient outcomes and cost-effectiveness of Elucigene FH20 and LIPOchip for the diagnosis of familial hypercholesterolaemia.

Searching
Twelve databases and trials registers – including MEDLINE and the Cochrane Central Register of Controlled Trials (CENTRAL) – were searched up to January 2011 for studies published since the year 2000 and reported in English. Conference proceedings were searched, references of included studies were checked and experts were contacted.

Study selection
Eligible studies assessed Elucigene FH20 and LIPOchip tests. Comparators were low-density lipoprotein cholesterol (LDL-C) concentration as part of the Simon Broome, Dutch or MEDPED criteria for diagnosis in index cases. In relatives, targeted gene sequencing and gender and age specific LDL-C criteria were used. The reference standard was comprehensive genetic analysis in combination with the diagnostic criteria. Eligible studies were direct head-to-head studies in which index, comparator and reference standard tests were all carried out in the same group of people; and randomised controlled trials (RCTs) that compared index and comparator tests in different people but in which everyone received the reference standard. Where there was insufficient evidence from these study types, diagnostic cross-sectional and case-control studies were also eligible. The population of interest was adults and children with a clinical diagnosis of familial hypercholesterolaemia and their first, second and third degree relatives. Simon Broome, Dutch or MEDPED criteria for diagnosis were all acceptable. Studies had to be conducted in secondary or tertiary care.

Adults, adolescents and children were enrolled in the included studies.

Two reviewers independently assessed the studies for inclusion in the review.

Assessment of study quality
Two reviewers independently assessed the methodological quality of the studies using a modified version of the QUADAS checklist. Three additional items assessed establishment of cut-off values before the start of the study, whether index test technology had changed since the study was carried out and whether a clear definition of what constituted a positive result was provided. Slightly different versions of the modified checklist were used for studies of Elucigene FH20 and LIPOchip; three items were coded not applicable for all LIPOchip and Elucigene FH20 studies and were applied only to LDL-C studies. Studies reported only in abstract were not assessed.

Data extraction
Data were extracted to enable construction of 2x2 tables of true and false positive and negative test results for index and comparator tests. Sensitivity, specificity and positive and negative likelihood ratios were calculated together with 95% confidence intervals.

One reviewer extracted data and these were checked by a second reviewer.

Methods of synthesis
The studies were combined in a narrative synthesis supported by forest plots of sensitivity and specificity. Planned meta-
analyses and calculation of summary receiver operating curves (SROC) curves were not undertaken due to insufficient data.

**Results of the review**

Fifteen diagnostic cross-sectional studies were included in the review. Three studies assessed Elucigene FH20 and five assessed LIPOchip. The other studies assessed LDL-C compared with genetic analysis (four studies) or reported age and gender-specific LDL-C for cascade testing of relatives (three studies).

Nine studies with full-text reports were assessed for quality. Participants were representative of those who would receive the test in practice. Studies that assessed Elucigene FH20 (one study) and LIPOchip (two studies) suffered from biases because not all patients received a reference standard test and patients did not receive the same reference standard test regardless of their index test result. Only one of the six studies of LDL-C showed these biases.

**Elucigene FH20**: Sensitivity ranged from 44% to 52% for Elucigene FH20. Sensitivity was 49% in those with a clinical diagnosis of definite familial hypercholesterolaemia compared with 40% in those with a diagnosis of possible familial hypercholesterolaemia. Specificity could not be calculated.

**LIPOchip**: Two versions were evaluated. Version 10 was designed to detect 189 UK-specific mutations and had sensitivity of 78.5%; specificity could not be calculated. Version 8 was designed to detect 251 mutations not specific to the UK and had sensitivity that ranged from 33.3% to 56.9% and specificity of 93.8%.

**LDL-C**: In two studies sensitivity of the test as part of the Simon Broome criteria was 90% and 93% but specificity was low at 28% and 29%. In cascade testing of relatives LDL-C testing using age and gender specific cut-offs, sensitivity ranged from 68% to 96%; specificity of between 84% and 93% was reported.

**Cost information**

Comprehensive genetic analysis remained the most cost-effective method of confirming a clinical diagnosis and testing relatives of an affected person. Probabilistic sensitivity analysis indicated that this was likely to be the most cost-effective strategy at all willingness-to-pay thresholds above £5,000, regardless of the age or prevalence rate of the population tested.

**Authors' conclusions**

In contrast with comprehensive genetic analysis, neither Elucigene FH20 nor LIPOchip can detect all cases of familial hypercholesterolaemia. Comprehensive genetic analysis was the most cost-effective method of confirmation of a clinical diagnosis of familial hypercholesterolaemia among Simon Broome possible or definite index cases and for cascade testing of first, second and third degree biological relatives.

**CRD commentary**

The review question and inclusion criteria were clear. The search was extensive and date limits were appropriate. The authors reported using methods designed to reduce reviewer bias and error at all stages of the review process. Appropriate methods were used to assess the validity of included studies. The decision not to proceed with the planned meta-analysis was appropriate given the limited information available.

The conclusions accurately reflect the limitations of the available evidence and may be considered reliable.

**Implications of the review for practice and research**

**Practice**: The authors did not state any implications for practice.

**Research**: The authors recommended a prospective multicentre study to compare Elucigene FH20, LIPOchip and LDL-C test in patients with a clinical diagnosis of familial hypercholesterolaemia based on Simon Broome criteria in which all test results were verified against the reference standard of comprehensive genetic analysis. Subgroup analysis in different ethnic groups, follow-up long enough to enable longer term clinical effectiveness to be assessed and an integrated economic evaluation were recommended for this study. Other recommendations were for investigation of the risks of familial hypercholesterolaemia onset in children, a systematic review of mutations that cause familial hypercholesterolaemia in the UK and specific ethnic populations, continuing research into finding novel familial hypercholesterolaemia-causing mutations and research on tests such as iPLEX.
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