NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Diagnostics Assessment Programme

Elucigene FH20 and LIPOchip for the diagnosis of familial hypercholesterolaemia

Final Scope
December 2010
Version 3

1. Introduction

The Medical Technologies Advisory Committee identified the Elucigene FH20 kit as potentially suitable for evaluation by the Diagnostics Assessment Programme (DAP) on the basis of a briefing note presented to the Committee in July 2010. The Elucigene FH20 kit is manufactured by Gen-Probe Life Sciences Ltd.

Scoping research carried out by the DAP team identified LIPOchip as a potential alternative test for inclusion in the evaluation. Attendees at the scoping workshop, held on 28 October 2010, supported the inclusion of LIPOchip in the evaluation. The LIPOchip test is manufactured by Progenika Biopharma S.A.

This scope outlines the approach for assessing the clinical and cost-effectiveness of Elucigene FH20 and LIPOchip for the diagnosis of familial hypercholesterolaemia. Assumptions made in the scope will be verified in the assessment.

A glossary is available in appendix 1.

2. Description of the technologies

Elucigene FH20 and LIPOchip have been designed to reduce the need for comprehensive genetic analysis for the detection of genetic mutations associated with familial hypercholesterolaemia. In doing so, they detect a reduced number of genetic mutations when compared to comprehensive genetic analysis.
2.1 Elucigene FH20

This section describes the Elucigene FH20 test based on the manufacturer’s notification to NICE. NICE has not carried out an independent evaluation of this description.

The Elucigene kit detects 20 mutations commonly found in the UK population. The kit uses ARMS™ allele specific amplification technology, which detects point mutations, insertions or deletions in the human LDLR, Apo B and PCSK9 genes in human whole blood. Fluorescent analysis is performed using capillary electrophoresis. The principle of ARMS™ allele specific amplification 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. 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, the individual has a confirmed diagnosis of FH. A potential limitation of this assay is that it only tests for 20 mutations associated with FH in the UK population (see section on ‘Target Condition – Genetic background’).

2.2 LIPOchip

LIPOchip is a genetic test that uses DNA array technology. The current version (v.10) of the chip tests for 189 mutations in the LDLR, APOB, PCSK9 genes known to occur in the UK population. The chip can detect point mutations, copy number changes and variation of number of copies of the LDLR gene. To process the chip a thermal cycler, Tecan hybridization station and glass-slide scanner are required. The manufacturer also offers a LIPOchip test processing service from its laboratory in Spain. Negative samples can be sequenced at additional cost. The data are analysed by the LIPOchip software which generates a report containing information on pathogenicity of detected mutations either based on scientific publications or the likelihood of being pathogenic based on a bioinformatics analysis.

A potential limitation of LIPOchip could be interpreting the results of the test; this will need further exploration in the assessment.
3. Target condition

*Condition background:* In some people, a high cholesterol level in the blood is caused by an inherited genetic defect known as FH, an autosomal dominant disorder. The disease is transmitted from generation to generation such that siblings and children of a person with FH have a 50% risk of inheriting the genetic defect. Most people with FH have inherited a defective gene for FH from only one parent, and are therefore heterozygous, and are at increased risk of cardiovascular disease. Rarely, a person will inherit the gene from both parents. This group of individuals has homozygous FH which has a significantly poorer prognosis than heterozygous FH. FH individuals have raised cholesterol levels from birth and it leads to an early development of atherosclerosis and cardiovascular disease.

*Prevalence and risk:* The prevalence of heterozygous familial hypercholesterolaemia in the UK population is estimated to be 1 in 500, which means that approximately 100,000 people in England are affected. The elevated serum cholesterol concentrations that characterise heterozygous FH lead to a greater than 50% risk of coronary heart disease by the age of 50 in men and at least 30% in women aged 60. Homozygous familial hypercholesterolaemia is rare, presents in children and is associated with early death from cardiovascular disease. Homozygous FH has an incidence of approximately one case per million. Currently, FH is an under-diagnosed condition as only 10-15% of individuals affected by FH have been identified in the English population.

*Genetic background:* The majority of genetic mutations associated with FH occur in the LDLR gene. Approximately 1200 unique mutations have been identified worldwide so far, of which over 200 have been reported in the UK population (other reliable sources suggest 130). FH causing mutations have also been found on the ApoB and PCSK9 genes. The frequency of FH causing mutations can vary from one population to another; which means that a test developed for one country may not be as effective if used in a different country. Furthermore, it may be possible for the frequency of mutations to vary amongst individuals of different ethnicities. The Centre for Cardiovascular Genetics (University College London) keeps an up-to-date database of genetic mutations associated with FH; information from the database can be used to estimate the frequency of FH mutations in the English population.
4. Care pathway

The care pathway for this evaluation is determined by the NICE clinical guideline on the identification and management of familial hypercholesterolaemia (CG71). Key highlights of CG71 are as follows:

4.1 Diagnosis

A diagnosis of FH should be made using the Simon Broome criteria, which include a combination of family history, clinical signs (specifically tendon xanthomata), cholesterol concentration and DNA testing (see appendix 2).

Healthcare professionals should inform people with a diagnosis of FH based on the Simon Broome criteria (see appendix 2) that they have a clinical diagnosis of FH.

To confirm a diagnosis of FH, healthcare professionals should undertake two measurements of LDL-C concentration because biological and analytical variability occurs.

Healthcare professionals should offer people with a clinical diagnosis of FH a DNA test to increase the certainty of their diagnosis and to aid diagnosis among their relatives.

Healthcare 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.

In children at risk of FH because of one affected parent, the following diagnostic tests should be carried out by the age of 10 years or at the earliest opportunity thereafter.

- A DNA test if the family mutation is known.
- LDL-C concentration measurement if the family mutation is not known. When excluding a diagnosis of FH a further LDL-C measurement should be repeated after puberty because LDL-C concentrations change during puberty.

4.2 Identifying people with FH using cascade testing

Healthcare 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.

Cascade testing using a combination of DNA testing and LDL-C concentration measurement is recommended to identify affected relatives of those index individuals 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. This should include at least the first- and second- and, when possible, third-degree biological relatives.
4.3 Management

Adults: Healthcare professionals should consider prescribing a high-intensity statin to achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline (that is, LDL-C concentration before treatment).

Children and young people: Lipid-modifying drug therapy for a child or young person with FH should usually be considered by the age of 10 years.

The decision to defer or offer lipid-modifying drug therapy for a child or young person should take into account:

- their age
- the age of onset of coronary heart disease within the family, and
- the presence of other cardiovascular risk factors, including their LDL-C concentration.

When the decision to initiate lipid-modifying drug therapy has been made in children and young people, statins should be the initial treatment.
5. Scope of the evaluation

5.1 Population

Adults and children who have a clinical diagnosis of FH (the index) based on the Simon Broome criteria, and targeted cascade testing of first-, second- and third-degree biological relatives.

NOTE: The individual initially identified with an FH causing mutation is known as the index (or proband). Biological relatives of the index are systematically tested for the inherited mutation/s using targeted cascade testing.

5.2 Interventions

1. Elucigene FH20, processed using fluorescent analysis or gel-based analysis
2. LIPOchip

NOTE: The Elucigene FH20 kit is available in two versions; based on the technology used to process the kit. Although the evidence for the gel-based analysis version is applicable to the fluorescent analysis version, any variations, for example sample throughput, between the two processing technologies need to be considered in the evaluation.

Data on the latest UK version of LIPOchip are lacking. Data on previous versions of the chip or estimates derived from the UCL FH database (or a combination of the two) may need to be considered in the assessment.

5.3 Comparators

1. LDL-C concentration measurement (part of the Simon Broome criteria)
2. Comprehensive genetic analysis + LDL-C concentration measurement of mutation negative individuals (part of the Simon Broome criteria) as described in CG71

NOTE: Recommendations from CG71 are noted in section 5.

Reference standard: comprehensive genetic analysis in combination with Simon Broome criteria. The techniques used in comprehensive genetic analysis have evolved over a short period of time. This may mean that data from studies using comprehensive genetic analysis as the reference standard may not have used the same techniques as other studies. If there is a significant difference in the diagnostic accuracy of the various definitions of comprehensive genetic analysis; this should be reflected in the assessment.

Comprehensive genetic analysis: for the purposes of this evaluation this 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) 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% FH mutations) and the PCSK9 p.Asp374Tyr gene mutation (~2% FH mutations). A limitation of this method is the cost associated with processing the sample. The term DNA diagnosis used in the clinical guideline is equivalent to comprehensive genetic analysis in this evaluation.

**LDL-C (low-density lipoprotein cholesterol) concentration measurement**: various cholesterol blood tests exist. Commonly, LDL-C concentration is estimated from a fasting blood sample using the Friedwald equation. Due to current NHS commissioning arrangements of genetic tests, the main test currently used to diagnose FH is LDL-C concentration measurement. There are some limitations of LDL-C measurement in terms of diagnostic accuracy. One such limitation is the overlap in LDL-C levels between affected and unaffected individuals, the cut-offs used can result in diagnostic ambiguity in an estimated 15% of children (aged 5-15 years) and in nearly 50% in adults aged (45-55 years).

As different methods can be used to provide a comprehensive genetic analysis and a LDL-C concentration measurement, these tests need to be explicitly defined in the assessment. Diagnostic strategies involving a combination of genetic tests may be possible (see section 8.1). Mutations that have been tested for earlier in a diagnostic strategy do not need to be tested for later on in the strategy if comprehensive genetic analysis is included. Therefore, the appropriate inclusion/exclusion of tests should be considered when defining comprehensive genetic analysis. For example, if the current version of LIPOchip detects deletions/duplications, then these genetic variations do not need to be tested for by comprehensive genetic analysis (i.e. the MLPA test may not be needed). The most commonly used methods/tests should form the basis of such definitions.

### 5.4 Outcomes

**QALYs associated with life-long treatment of FH individuals with cholesterol lowering therapy and therefore, avoidance of cardiovascular related events.**

**Final health outcomes**: the avoidance of CHD events such as angina, myocardial infarction, stroke and death will be the main driver of final health outcomes for FH individuals. Lipid-lowering drug therapy by the statin class of drugs is effective in FH individuals and is associated with reduced CHD morbidity and mortality. The QALYs gained from the use of statins/ezetimibe therapy in the treatment of FH individuals needs to be modelled. Further considerations include: 1) CHD risk and therefore individual outcomes vary by age and gender; 2) evidence on the use of statins in children needs to be assessed; 3) some individuals identified with a DNA mutation may already be on cholesterol lowering therapy. Equally, individuals that have been confirmed not to have a DNA mutation may still require cholesterol lowering therapy based on a 10 year risk of CVD greater than 20% (current NICE guidance TA94); and 4) the impact of the diagnostic test on treatment adherence should be accounted for; 5) the type of mutation identified and severity of FH may impact treatment choice.
and, subsequently, QALYs gained; the evidence was found to be inconclusive in CG71 so the literature should be re-examined to ascertain if this is still the case; and 6) data from Versmissen et al. 2008, a long-term cohort study, was not available for use in CG71 to assess the efficacy of statins in FH. The benefit of cholesterol lowering therapy should be checked for consistency with data from Versmissen et al. 2008. If data are available, which supersedes Versmissen et al. 2008, these should be used instead.

Utility of diagnostic information: diagnostic information can lead to changes in an individual's utility above and beyond any effect on their clinical management. For example, parents place a positive value on knowing the diagnosis in a child with a genetic condition, or the psychological impact of a definitive genetic diagnosis. This may be measured in part by the increased adherence to treatment or lifestyle changes; however, the total impact of diagnostic information on an individual's utility may not be captured in full by these factors alone. For example, there may be additional utility in non-health (and health) outcomes such as family planning and empowerment. Equally, there may be disutility if the psychosocial impacts of having such diagnostic information are negative.

As the type of diagnostic information generated from the tests considered in the scope varies (e.g. genetic and non-genetic diagnosis), such differences may impact an individual's utility and consequently may alter the ICERs for each diagnostic strategy. Finding or generating suitable data on the value of diagnostic information (health and non-health related) and the subsequent impact on QALYs/ICERs is highly desirable.

5.5 Health care setting

Secondary and tertiary care

NOTE: Data on identifying individuals with FH using genetic testing are available for the secondary care environment. In addition, CG71 recommends “Healthcare 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”.

5.6 Additional considerations

The diagnostic tests included in the evaluation should be assessed for their technical robustness (analytical validity).

Pathogenicity of mutations, that is, the link between a genetic mutation and the resulting clinical presentation of disease is an area of significant uncertainty. Definitions of pathogenicity and the methods used to determine the clinical significance of genetic mutations are subject to variation. The implications of this variation need to be fully understood in the assessment. Guidelines for the interpretation and reporting of unclassified variants in clinical molecular genetics produced by the Clinical Molecular Genetics Society aim to provide a set of agreed standards for diagnostic laboratories (web link).
6. **Cost considerations**

6.1 **Diagnostic technologies**

Based on manufacturer input, the equipment required to process the Elucigene FH20 and LIPOchip tests are assumed to be readily available in most genetic laboratories in England; these assumptions need to be verified in the assessment. In addition, the LIPOchip test should be assessed using both processing options: 1) processing the chip in a genetics lab(s) in England; and 2) processing the chip via the manufacturer service in Spain. If there are non-recurrent set-up costs associated with Elucigene FH20 or LIPOchip, these need to be understood in relation to a potentially optimal implementation strategy as this may impact costs used in the assessment (see section on 'Implementation').

Equipment needed to process comprehensive genetic analysis and LDL-C concentration measurements are already available in the NHS, therefore, equipment costs associated with implementation are unlikely to be incurred.

Costs associated with testing the index individual and relatives will vary and need to be fully understood. Resource utilisation associated with the processing of genetic tests and the necessary training should be considered. As a standard NHS tariff does not exist for genetic tests, the resource utilisation costs may not reflect actual prices charged by genetics laboratories across England.

There are a limited number of genetic laboratories to process the tests and the nature of FH means test results are not time sensitive (from a condition perspective). Therefore, it is assumed that genetic laboratories can batch tests for maximum efficiency. As a result, all primary cost estimates should reflect operation at maximum efficiency (i.e. minimum costing) and a sensitivity analysis should explore less efficient operation.

6.2 **Treatments**

The patents of some branded statins (in particular, atorvastatin – used in the CG71 economic models) are due to expire during the course of this evaluation. The expected/resulting impact on costs should be accounted for in the assessment.

7. **Modelling approach**

The main structure of the model should be based around the care pathway and related considerations (e.g. individuals with no mutation and elevated LDL-C levels) described in CG71 and should take into account technology appraisals of statins/ezetimibe therapy, cardiovascular risk assessment and any other existing NICE guidance that is applicable (see appendix 3). The assumptions described below should be verified in the assessment.
**Model aim**: to compare the costs and benefits of a range of diagnostic strategies involving Elucigene FH20 and alternative tests used to confirm the clinical diagnosis of FH in index individuals and identify their relatives with FH.

**Care pathway**: determined by the clinical guideline on the identification and management of FH.

**Model structure**: a lack of direct evidence of the relative effectiveness and cost–effectiveness of the diagnostic tests means a linked evidence approach should be used in the modelling. That is, to relate intermediate outcomes (i.e. the diagnostic accuracy) of plausible diagnostic strategies, involving genetic/LDL-C tests, to changes in management and changes in final health outcomes. The model should be designed to allow the inclusion of other diagnostic tests that may be available in the future.

Although it is acknowledged the treatment strategy may vary between homozygous and heterozygous FH individuals, modelling these groups independently is unnecessary as the prevalence of homozygous FH is significantly lower. However, a qualitative account can be made to distinguish between those tests that can and cannot diagnose homozygous FH.

CG71 modelled individuals based on the type of diagnosis from the Simon Broome criteria (i.e. definite, possible and those that have FH but do not meet the Simon Broome criteria). This level of detail will be of value to this assessment.

**Extant models**: CG71 has existing economic models for 1) use of high intensity statin compared to low intensity statin in the management of FH patients; and 2) cascade testing for FH using DNA testing and low density lipoprotein (LDL) Cholesterol methods. Any existing models used in this assessment need to be assessed for relevance and modified as appropriate; please refer to section 5.4 on outcomes and section 6.2 on costs.

The reference case as described in the NICE Guide to the Methods of Technology Appraisal is applied to the assessment of diagnostic technologies.

### 7.1 Modelling index individuals

Individuals enter the model with a clinical diagnosis of FH (using the Simon Broome criteria), likely based on a LDL-C cholesterol measurement. The UK FH Cascade Audit Project has confirmed that, based on the Simon Broom criteria, 30% of the patients currently being treated in lipid clinics have DFH and 60% have PFH while 10% fail to meet either criterion. Individuals are then offered genetic and LDL-C tests to confirm the diagnosis. Genetic tests allow for the possibility of making an unequivocal diagnosis of FH and for identifying the family mutation which can be used for targeted cascade testing of relatives.

As the number of mutations tested for (and therefore the associated costs and number of individuals identified) by each genetic test varies, a number of possible diagnostic strategies may emerge.
Diagnostic strategies for identifying a genetic mutation (or LDL-C level) in index individuals include:

Table 1: Diagnostic strategies for identifying a genetic mutation (or LDL-C level) in index individuals

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>Elucigene</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>L IPOchip</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>Comprehensive genetic analysis (CGA)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>Elucigene then LIPOchip for negative</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>Elucigene then CGA for negative</td>
<td>Treatment decision</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>LIPOchip then CGA for negative</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>Elucigene then LIPOchip for negative then CGA negative</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>Elucigene then MLPA for negative</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>LIPOchip then MLPA for negative</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>Elucigene then LIPOchip for negative then MLPA for negative</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>LDL-C test</td>
<td></td>
</tr>
</tbody>
</table>

Key: Negative = individuals with a negative diagnosis  
MLPA = multiplex ligation-dependent probe amplification

The strategies above assume that individuals who receive a positive result move to stage 3 for a treatment decision (there may be some exceptions). Individuals who receive a negative diagnosis, where applicable, may be tested by another genetic test. Also, it is assumed that LIPOchip is unable to accurately detect duplications/deletions and the MLPA test will still be required. This assumption should be explored in the analysis.

As Elucigene FH20 and LIPOchip test for a specific set of mutations, these tests can only be used to identify individuals that have those genetic variations. Therefore, any strategy with Elucigene FH20 or LIPOchip may include further tests for those individuals who receive a negative diagnosis as this does not mean they do not have FH (as the individual could have a genetic mutation not tested for in Elucigene FH20/LIPOchip). In addition, individuals who have tested positive on a genetic test may need further tests in certain circumstances. For example, the LIPOchip test provides results on the pathogenicity of the identified mutation and some of the mutations may or may not be pathogenic. Some individuals may require further investigation to confirm whether or not the mutation will lead to FH.

Further strategies may be added if identified during the assessment.

7.2 Modelling cascade testing
7.2.1 Index individuals with an identified genetic mutation
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The genetic test used for cascade testing relatives of the index individual may vary from the test initially used in the index. For example, if the family mutation is identified in an index individual using LIPOchip, a different genetic test may be used to test for the family mutation in relatives. The reason for doing this is that once a mutation is identified with LIPOchip, a more specific genetic test can be used to locate the same mutation in relatives at a reduced cost per test. This avoids unnecessarily testing for the full range of mutations available in the LIPOchip test. Relatives of the index individual are offered both genetic and LDL-C tests in cascade testing. In relatives who receive a genetic test and are mutation negative, cascade testing stops.

Diagnostic tests that may be used for cascade testing include:

Table 2: Diagnostic tests that may be used for cascade testing relatives of an index individual with an identified FH mutation

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Test used to identify a mutation in the index individual</th>
<th>Test used to find the family mutation in relatives (cascade testing)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Elucigene FH20</td>
<td>Elucigene FH20</td>
</tr>
<tr>
<td>2</td>
<td>LIPOchip</td>
<td>Targeted sequencing</td>
</tr>
<tr>
<td>3</td>
<td>Comprehensive genetic analysis</td>
<td>Targeted sequencing</td>
</tr>
</tbody>
</table>

Targeted sequencing is used to describe the genetic test for sequencing a specific part of the gene where the family mutation is found. This is at a reduced cost to comprehensive genetic analysis and likely to be at a reduced cost when compared to LIPOchip. The cost of Elucigene FH20 is likely to be lower than targeted sequencing. If this is the case, Elucigene FH20 can be used to cascade test from a small proportion of index individuals tested by LIPOchip and comprehensive genetic analysis who test positive for a mutation tested for by Elucigene FH20.

7.2.2 Index individuals without an identified genetic mutation

CG71 recommends ‘In the absence of a DNA diagnosis, cascade testing using LDL-C concentration measurements should be undertaken to identify people with FH’. That is, index individuals are tested by a genetic test. If the index has an identified genetic mutation for FH, cascade testing is undertaken using the family mutation (as described in 7.2.1). If the index does not have a genetic mutation for FH (either as a result of the genetic test or of not being tested at all by a genetic test), cascade testing is undertaken using the LDL-C test. These individuals will need to be considered in the modelling.

8. Equality issues
The most common mutations in the European Caucasian population have been used to develop the Elucigene FH20 kit. The prevalence of mutations may vary according to ethnicity and it is possible that some mutations that are more common in subpopulations may not be detected by the Elucigene FH20 test. The literature review performed by the assessment group should provide further information on this issue.

9. Implementation

NHS clinical genetic services including molecular genetic testing are commissioned through specialised commissioning, for example Specialised Commissioning Groups in England. However, genetic tests such as Elucigene FH20 and LIPOchip will be used by clinical services that are funded through mainstream clinical services commissioning, for example led by primary care trusts (PCTs) in England. Therefore FH testing will not normally be commissioned as part of specialised services. Implementation tools developed by NICE to support this guidance will aim to inform PCT commissioners and assist them in developing the necessary diagnostic services, and will be developed in the context of related NICE guidance, including CG71 - Identification and management of familial hypercholesterolaemia. Commissioners will need to know whether there are significant non-recurrent set-up costs associated with the introduction of Elucigene FH20 or LIPOchip, particularly where these are likely to influence the location of services or the size of population they would need to serve. In developing implementation support, NICE will consider the experiences of the FH programmes in Wales (web link) and Scotland (web link), and the primary care service framework for FH produced by NHS Primary Care Commissioning (web link).
Appendix 1 – Glossary

**Autosomal dominant pattern of inheritance (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, onto each of their children.

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

**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 FH are tested for the condition as are their relatives; ideally cascade testing should be undertaken in first-, second- and third-degree relatives. For FH the test employed is measurement of (LDL) cholesterol in the blood, and/or a DNA test if a disease-causing mutation has been identified in the proband/index.

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

**Children/young people** ‘Children’ refers to persons younger than 10 years; ‘young people’ refers to persons from 10 years of age up to the age of 15 years. The definitions used here are not prescriptive and healthcare professionals are expected to exercise their judgement and consider the wishes of the individual, and their families or carers when interpreting these terms in individual instances.

**Family history** The structure and relationships within the family that relates information about diseases in family members.

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

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

**Homozygous FH** Very high LDL cholesterol level in the blood caused by an inherited mutation from both parents. Where a person inherits exactly the same affected gene from both parents this is called truly “homozygous” FH. When the mutations in the LDL receptor gene (or equivalent) are different, this state is called ‘compound heterozygous’. In general, the overall effect in both states is similar in that LDL cholesterol concentrations are very high. Both groups of individuals have the same clinical pattern and high risk of cardiovascular disease.
**Index individual** (synonymous with ‘proband’) The original individual (proband) who is the starting point for follow-up of other members of a family when investigating for possible causative genetic factors of the presenting condition.

**LDL-C** Low density lipoprotein cholesterol.

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

**Pathogenicity** For the purposes of this evaluation, pathogenicity is defined as the probability of a genetic mutation resulting in the clinical presentation of FH (characterised by raised cholesterol levels).

**Proband** The affected (index) individual through whom a family with a genetic disorder is ascertained.

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

**Specialist** One who has expertise in a particular field of medicine by virtue of additional training and experience. For this guideline, we use specialist to refer to a healthcare professional with an expertise in FH.

**Targeted cascade testing** A mechanism for identifying individuals at increased risk of developing a particular condition. In the case of FH, targeted cascade testing of relatives of positively diagnosed individual aims to provide a greater rate of case identification than general population screening.

**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 FH which most frequently affects the Achilles tendons but can also involve tendons on the back of the hands, elbows, and knees.

**Third-degree relative** A person’s biological great grandparent, great grandchild, great aunt, great uncle, first cousin, grand nephew or grand niece.
Simon Broome Diagnostic criteria for index individuals and relatives

Diagnostic criteria

Diagnose a person with **definite** familial hypercholesterolaemia (FH) if they have:

- cholesterol concentrations as defined in table 1 and tendon xanthomas, or evidence of these signs in first- or second-degree relative

  or

- DNA-based evidence of an LDL-receptor mutation, familial defective apo B-100, or a PCSK9 mutation.

Diagnose a person with **possible** FH if they have cholesterol concentrations as defined in table 1 and at least one of the following.

- Family history of myocardial infarction: aged younger than 50 years in second-degree relative or aged younger than 60 years in first-degree relative.

- Family history of raised total cholesterol: greater than 7.5 mmol/l in adult first- or second-degree relative or greater than 6.7 mmol/l in child, brother or sister aged younger than 16 years.

<table>
<thead>
<tr>
<th>Table 1 Cholesterol levels to be used as diagnostic criteria for the index individual</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Child/young person</strong></td>
</tr>
<tr>
<td>Total cholesterol</td>
</tr>
<tr>
<td>&gt; 6.7 mmol/l</td>
</tr>
<tr>
<td>&gt; 7.5 mmol/l</td>
</tr>
</tbody>
</table>

*levels either pre-treatment or highest on treatment.*

LDL-C, low-density lipoprotein cholesterol.
Appendix 3 – Extant NICE guidance

Identification and management of familial hypercholesterolaemia. NICE clinical guideline 71 (2008)

Statins for the prevention of cardiovascular events in people at increased risk of developing cardiovascular disease or those with established cardiovascular disease. NICE technology appraisal 94 (2006).


Appendix 4 – Literature


