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Cost-utility analysis of searching electronic health records and cascade testing to identify and diagnose familial hypercholesterolaemia in England and Wales

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ABSTRACT

Background and aims: The cost effectiveness of cascade testing for familial hypercholesterolaemia (FH) is well recognised. Less clear is the cost effectiveness of FH screening when it includes case identification strategies that incorporate routinely available data from primary and secondary care electronic health records.

Methods: Nine strategies were compared, all using cascade testing in combination with different index case approaches (primary care identification, secondary care identification, and clinical assessment using the Simon Broome (SB) or Dutch Lipid Clinic Network (DLCN) criteria). A decision analytic model was informed by three systematic literature reviews and expert advice provided by a NICE Guideline Committee.

Results: The model found that the addition of primary care case identification by database search for patients with recorded total cholesterol >9.3 mmol/L was more cost effective than cascade testing alone. The incremental cost-effectiveness ratio (ICER) of clinical assessment using the DLCN criteria was £3254 per quality-adjusted life year (QALY) compared with case-finding with no genetic testing. The ICER of clinical assessment using the SB criteria was £13,365 per QALY (compared with primary care identification using the DLCN criteria), indicating that the SB criteria was preferred because it achieved additional health benefits at an acceptable cost. Secondary care identification, with either the SB or DLCN criteria, was not cost effective, alone (dominated and dominated respectively) or combined with primary care identification (£63, 514 per QALY, and £82,388 per QALY respectively).

Conclusions: Searching primary care databases for people at high risk of FH followed by cascade testing is likely to be cost-effective.

1. Introduction

Familial hypercholesterolaemia (FH) is characterised by an inherited genetic mutation which causes a high cholesterol concentration from birth. People with FH have a higher risk of coronary heart disease (CHD), particularly at younger ages. [1] Once diagnosed, lifestyle changes and lipid modification treatment substantially reduce the risk of CHD. [2,3].

It is estimated that between 115,000 and 267,000 people in England and Wales have FH but only 18,000 are currently diagnosed, representing an opportunity to substantially reduce the mortality and morbidity associated with the disease. [1,4,5] Cascade testing is recommended by clinical guidelines to identify people with FH who are currently undiagnosed because it has been shown to be effective and cost effective. [6–9] Cascade testing is the process of inviting relatives of people currently diagnosed with FH to undergo genetic testing to see if they carry the family mutation. However, it has been estimated that only half of all carriers are

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likely to be identified using this strategy. [5].

New evidence has emerged on the effectiveness of searching primary care and secondary care databases for people at high risk of FH based on routinely collected information on biochemical tests, clinical signs including xanthomas, personal history of cardiovascular disease (CVD) and family medical history. [10–16] Examples of biological markers are high LDL-cholesterol (LDL-C) and high total cholesterol. Other characteristics may include a family history of early CHD. Based on these characteristics, the clinician may assess the patient against standard FH diagnostic criteria, usually the Simon Broome (SB) or Dutch Lipid Clinic Network (DLCN) criteria. Those identified with possible FH would be referred to a lipid clinic for specialist consultation and genetic testing.

The cost effectiveness of searching databases should be established prior to wider adoption because of the resource impact on healthcare providers and the National Health Service (NHS). Activities that require resource reallocation include informatics setup, training staff in GP surgeries, contacting patients to invite them for further assessment, lipid clinic consultations, genetic testing and treatment following a positive diagnosis. Whether this resource impact is cost effective is influenced by the likelihood people identified for further assessment actually have FH, the diagnostic accuracy of the diagnostic criteria, the take up rates of clinical assessment and cascade testing, and the costs and health benefits associated with long term lipid modification treatment.

Recommendations in the original NICE guideline were based on economic modelling of cascade testing only conducted by Nherera et al., in 2011. [6] The 2017 update identified studies supporting the cost effectiveness of cascade testing but revealed that the cost effectiveness of new index case identification in primary care or secondary care had not been investigated. [6–9,17] The present economic analysis was developed to provide this evidence.

2. Materials and methods

2.1. Population and subgroups

There are six groups of people that have the potential to come in to contact with the interventions: current index cases, potential new index cases from primary or secondary care, and the relatives of people in each of these three groups.

Current and potential new index cases, consisting of the groups of people with a current clinical diagnosis, people identified in a primary care database as requiring further investigation, and people identified in a secondary care database as requiring further investigation, were further stratified to differentiate people that had a monogenic cause of their hypercholesterolaemia (autosomal dominant FH caused by mutations in the *LDLR*, *APOB* and *PCSK9* genes) and those with multifactorial hypercholesterolaemia. Within the multifactorial group will be individuals with a polygenic aetiology due to co-inheritance of common LDL-C-raising variants ("polygenic hypercholesterolaemia"). [18,19] Genetically confirmed monogenic FH is associated with a greater risk of CHD compared with polygenic hypercholesterolaemia. [20,21] For the purposes of modelling, a simplifying assumption was made that relatives cannot carry both monogenic FH and polygenic hypercholesterolaemia. Long term modelling was conducted including cohorts of males and females beginning between age 40 and 70 that were broadly representative of the UK population within these age bands.

2.2. Strategies compared

The strategies that were compared in the analysis are summarised in Table 1. The diagnostic pathway and resource use associated with each strategy was mapped in consultation with the NICE Guideline Committee. [17] The full description of each strategy along with diagrams in the form of a decision tree are provided in the Supplementary Material.

The NICE guideline committee selected the SB and DLCN criteria as the most widely used clinical assessment tools out of nine available. [22] Onward referral for genetic testing is typically considered when a patient has 'possible' or 'definite' FH on the SB criteria or a score greater than 5 on the DLCN criteria. [1] Genetic testing is the gold standard for diagnosing monogenic FH.

2.3. Modelling approach

The setting of interest is the NHS in England and Wales. Costs were derived using the perspective of the NHS and include direct medical costs, such as the staff cost of searching databases, conducting clinical assessment in primary or secondary care settings and genetic testing. The perspectives of people with FH and multifactorial hypercholesterolaemia were adopted for health

Table 1
Characteristics of strategies compared in the analysis.

Strategy	Genetic cascade testing	Search primary care database	Search secondary care database	SB criteria for clinical assessment (base case possible & definite)	DLCN criteria for clinical assessment (base case score > 5)
Strategy 1	✘	✘	✘	✘	✘
Strategy 2	✓	✘	✘	✘	✘
Strategy 3	✓	✓	✘	✓	✘
Strategy 4	✓	✓	✘	✘	✓
Strategy 5	✓	✘	✓	✓	✘
Strategy 6	✓	✘	✓	✘	✓
Strategy 7	✓	✓	✓	✓	✘
Strategy 8	✓	✓	✓	✘	✓
Strategy 9	✓	✓	✘	✘	✘

SB: Simon Broome; DLCN: Dutch Lipid Clinic Network.
[a] Cascade testing offered to the relatives of currently diagnosed index cases only.