Alternative cascade-testing protocols for identifying and managing patients with familial hypercholesterolaemia: systematic reviews, qualitative study and cost-effectiveness analysis

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Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the tool kit on the NIHR journals Library report publication page at https://doi.org/10.3310/CTMD0148.

Primary conflicts of interest: Nadeem Qureshi has received grants from the National Institute for Health and Care Research (NIHR) School for Primary Care Research (SPCR) and the Medical Research Council (MRC) (Newton–Ungku Omar Fund), has received honoraria from Amgen Inc. (Thousand Oaks, CA, USA) for lectures on familial hypercholesterolaemia, is a member of the board for the NIHR SPCR (2021 to present) and is a member of the Medical, Scientific and Research Committee of HEART UK. Bethan Woods reports membership of the NIHR Health Technology Assessment Clinical Evaluation and Trials Funding Committee (2020–24). Jo Leonardi-Bee has received a grant from the MRC to conduct research in the field of familial hypercholesterolaemia. Stephen Weng was part of an institution that received grants from the NIHR SPCR for research related to familial hypercholesterolaemia, has received consulting fees from the Academic Advisory Committee for RoadtoHealth Ltd (Hailsham, UK), has received honoraria and travel fees from Amgen Inc. for lectures on familial hypercholesterolaemia, was previously a committee member for the Medicines and Healthcare products Regulatory Agency Clinical Practice Research Datalink Independent Scientific Advisory Committee and is currently employed by Janssen R&D, High Wycombe, UK. Steve E Humphries has received support from the British Heart Foundation (PG 008/08); is the director of the UK Familial Hypercholesterolaemia Paediatric Register, which has received support from a grant from the International Atherosclerosis Society (Pfizer number 24052829); and is a medical director and minor shareholder of the University College London Business Ltd spinout company StoreGene (London, UK), which offers deoxyribonucleic acid (DNA) testing for individuals with familial hypercholesterolaemia. Kate Haralambos has received payment for PASS (PASS Software, Rijswijk, the Netherlands) clinical data entry and for extracting and processing data. Dev Datta has received personal honoraria from Daiichi Sankyo Company, Ltd (Tokyo, Japan), Pfizer Inc. (New York City, NY, USA), Ionis Pharmaceuticals, Inc. (Carlsbad, CA, USA), Amgen Inc., Akcea Therapeutics, Inc. (Ionis Pharmaceuticals, Inc.), Novartis AG (Basel, Switzerland) and Amryt Pharma plc (Dublin, Ireland), which are all manufacturers in the field of lipidology. Zosia Miedzybrodzka has received payment for arranging data extraction and for presenting data in Scottish health data Safe Haven (Grampian Data Safe Haven, University of Aberdeen) and has received funding from Amgen Inc. and Akcea Therapeutics, Inc. Joe Kai is a member of the NIHR SPCR board (2015 to present).

Published October 2023
DOI: 10.3310/CTMD0148

Scientific summary

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Health Technology Assessment 2023; Vol. 27: No. 16
DOI: 10.3310/CTMD0148

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

Cascade testing among relatives of index cases is the most efficient and cost-effective approach to identifying people with familial hypercholesterolaemia (FH). The cascade-testing protocol starts with identifying the first patient in the family with FH (index case) and is followed by one of three approaches: indirect approach, whereby the patient with FH contacts their relatives; direct approach, whereby the genetic specialist contacts the relatives; or a combination of both direct and indirect approaches.

The National Institute for Health and Care Excellence (NICE) recommend that, once FH is genetically confirmed in index cases, FH cascade testing should be offered to first- then second-degree relatives using streamlined genetic testing for pathogenic variants identified in the index case. Alternative protocols include testing of first- and second-degree relatives simultaneously, rather than sequentially, and also consider the role of non-genetic markers for FH status among relatives. However, it is currently unclear how FH cascade-testing services should be configured to improve the number of relatives identified while offering value for money.

Aim

The aim of this study was to identify the most cost-effective protocol for cascade testing for FH.

This aim was answered through three inter-related objectives:

1. to determine the yield of cases, treatment patterns, and short- and long-term outcomes for FH patients
2. to evaluate the cost-effectiveness of alternative protocols for FH cascade testing using data from services in two UK regions, the literature and linkage of national clinical databases
3. to qualitatively assess the acceptability of cascade-testing protocols to individuals and families with potential and confirmed FH, and to health-care providers.

The yield of cases was assessed through systematic reviews and analysis of PASS (PASS Software, Rijswijk, the Netherlands) hospital FH databases, whereas treatment patterns and short- and long-term outcomes of FH were investigated through systematic reviews, analysis of a specialist FH register and the Clinical Practice Research Datalink (CPRD)–Hospital Episode Statistics (HES) databases. The cost-effectiveness analyses incorporated the previous analyses, together with stakeholder input and data from the Dutch FH service. Finally, acceptability of the cascade-testing approaches were evaluated through semistructured interviews with FH patients, their relatives and health-care professionals.

Methods and results

Yield of cases

Effectiveness of contact strategies for cascade testing among relatives for familial hypercholesterolaemia (systematic review 1)

This review was performed to quantify the effectiveness of different contact approaches in cascade testing. A total of 2347 titles and abstracts were screened, with 217 screened at full-text stage. Twenty-four non-comparative studies were included, of which 12 used a direct approach, 7 used an indirect approach and 5 used a combination of both. Although evidence is very limited, the combined approach

resulted in more relatives being tested for FH [40%, 95% confidence interval (CI) 37% to 42%, one study] than either the direct or indirect approaches (direct: 33%, 95% CI 28% to 39%, one study; indirect: 34%, 95% CI 30% to 37%, two studies).

Diagnostic accuracy of clinical and biochemical criteria and scoring systems based on these characteristics to diagnose relatives of index cases with familial hypercholesterolaemia (systematic review 2)

This review aimed to assess the diagnostic accuracy of clinical and biochemical tests among relatives of index cases with genetically confirmed FH. Nine studies met the inclusion criteria. None of the studies reported the low-density lipoprotein cholesterol (LDL-C) (or other biochemical characteristics') distribution for relatives with and relatives without FH by age and sex; therefore, they could not be used to directly inform the cost-effectiveness analysis. The included studies suggested that the Dutch national FH cascade screening programme had relevant data for our research. The data controllers of the Dutch programme provided aggregate data on the distributions of LDL-C of relatives tested, which were used to inform the cost-effectiveness analysis of alternative cascade-testing protocols.

Yield of cases in PASS Welsh and Wessex familial hypercholesterolaemia service databases

We analysed a large sample of index cases (Wales, $n = 2618$; Wessex, $n = 1116$) and relatives (Wales, $n = 3815$; Wessex, $n = 2143$) within these FH services to characterise individuals and estimate the yield of different cascade-testing protocols in the subsequent cost-effectiveness modelling. The performance of alternative criteria for selecting index cases for genetic testing was also assessed, and predictors of cascade testing success were evaluated using logistic regression.

In Wales, female relatives, first-degree relatives of index cases and relatives contacted directly by the service were more likely to complete cascade testing ($p < 0.01$). In Wessex, females were more likely to complete cascade testing ($p < 0.01$). For relatives, approximately one-quarter of cases were deemed to be out of the area. Cardiovascular disease (CVD) history was more common in older age groups and among those with FH, lipid-lowering treatment (LLT) prior to the cascade was more common among relatives with CVD, and relatives without a CVD history were more likely to be treated prior to cascade testing if they had FH.

Treatment patterns and short- and long-term outcomes of familial hypercholesterolaemia cases

The search of relevant systematic reviews looking at the effectiveness of LLTs to prevent CVD in adults identified 14 systematic reviews; none of these met the methodological quality standards to be included in the review of reviews. Our analysis of 2879 individuals with a recorded diagnosis of FH in the primary care data set (CPRD) indicated that only 26% of these individuals are treated with LLT within 2 years of their diagnosis, and, of those who are treated, < 30% achieve the NICE-recommended reductions in LDL-C (≥ 50% reduction).

Cardiovascular outcomes in FH cases were evaluated in the primary care CPRD data and in the specialist FH (Simon Broome) register. Both data sets were linked to the secondary care data set, HES.

Cardiovascular disease outcomes using the Clinical Practice Research Datalink (primary–secondary care linked data set)

Patients with FH codes in primary care records and no pre-existing CVD recorded were identified ($n = 14,097$) and matched with randomly identified non-FH controls ($n = 42,506$). Incidence rates of coronary heart disease (CHD), stroke/transient ischaemic attack (TIA) and peripheral vascular disease (PVD) were higher among FH cases; overall CVD risk was increased [hazard ratio (HR) 9.14, 95% CI 8.55 to 9.76; $p < 0.001$], as was the risk of CHD (HR 10.63, 95% CI 9.82 to 11.49; $p < 0.001$), stroke/TIA (HR 6.74, 95% CI 5.84 to 7.77; $p < 0.001$) and PVD (HR 7.17, 95% CI 6.08 to 8.46; $p < 0.001$).

In addition, CVD risk modelling was conducted to inform the cost-effectiveness analysis. This analysis included 2135 individuals with a recorded diagnosis of FH in primary care, with linked hospital data and who had received LLT following diagnosis. After 20 years of follow-up, parametric modelling predicted the average risk of a first major non-fatal CVD event or cardiovascular-related death to be 11%. History of CVD was identified as a key prognostic variable, with age, sex and raised pre-treatment LDL-C also being important indicators.

Cardiovascular disease outcomes in secondary care using a national familial hypercholesterolaemia register

Of 3553 FH individuals in the Simon Broome Register, 2988 (52.5% women) had linked HES records. Standardised morbidity ratios (SMbRs), compared with an age- and sex-matched UK general practice population, were calculated for composite cardiovascular outcomes (first HES outcome of CHD, myocardial infarction, stable or unstable angina, stroke, TIA, PVD, heart failure or coronary revascularisation interventions). The SMbR for FH patients was 7.17 (95% CI 6.79 to 7.56). The SMbR for CHD was substantially higher for women than for men aged 30–50 years [19.66 (95% CI 16.78 to 23.04) and 12.54 (95% CI 11.22 to 14.01), respectively].

Cost-effectiveness of cascade testing

Cost and health benefits of diagnosis of people with familial hypercholesterolaemia in the long term

We developed a new cost-effectiveness model to estimate the impact of FH diagnosis and treatment on health outcomes and to inform the cost-effectiveness analysis of alternative cascade protocols.

The cohort Markov model takes the UK NHS perspective over a lifetime time horizon and discounts future health outcomes and costs to their present value at 3.5%. The model is informed by the analysis of time to CVD event and effect of treatment on LDL-C using the CPRD/HES primary–secondary care linked data for patients with a coded diagnosis of FH in primary care. We estimated the counterfactual risk had they not been treated, considering the increased effect of LDL-C on CVD risk over time (known as 'cholesterol burden').

The cost-effectiveness model found that the net health gain from diagnosis ranged from −0.27 to 2.51 quality-adjusted life-years (QALYs) at the threshold of £15,000 per QALY gained. The net health gain is positive (i.e. diagnosis is cost-effective) among people with pre-treatment LDL-C of ≥ 2.5 mmol/l or who have prior CVD history. In general, the net health gain of diagnosis is greater for males, people with higher pre-treatment LDL-C and people with prior CVD history at diagnosis. The main areas of uncertainty related to the effects of 'cholesterol burden' and of age on long-term CVD risk, and the effect of diagnosis (and management) on LDL-C.

Cost-effectiveness of alternative cascade-testing protocols for familial hypercholesterolaemia

We developed a new decision model to simulate cascade-testing protocols and predict their implications for long-term health outcomes and costs. The decision tree was informed by the analysis of data from the PASS data sets, data on LDL-C of relatives with and relatives without FH from the Dutch FH service, and the long-term health outcomes and costs estimated by our cost-effectiveness model of diagnosis and treatment, together with other sources of data and input from our stakeholder group. The model takes the UK NHS perspective and calculates the proportion and number of relatives diagnosed, the costs of cascade testing, and cost-effectiveness at the thresholds of £15,000 and £20,000 per QALY gained.

The protocols on the cost-effectiveness frontier generally involved starting cascade testing from genetically confirmed index cases and having the service contact first- and second-degree relatives simultaneously and directly. The most cost-effective protocol diagnoses relatives according to treatment status, LDL-C and age, with some having confirmatory genetic testing. Per index family assessed for

cascade, the cost-effective protocol diagnoses 52% of relatives with the disease, at a cascade cost of £536 and with an incremental cost-effectiveness ratio of £13,996 per QALY gained. The cost-effective protocol using the same genetic testing strategy for all relatives regardless of age (the harmonised cost-effective protocol) achieves similar outcomes and may be preferable if additional nurse time (unaccounted for here) is required to implement a testing approach that differs according to relatives' age. Furthermore, offering genetic testing to all relatives diagnoses more relatives (56%), but it is not cost-effective because of the additional costs, although the difference with the cost-effective protocol is small (cascade cost of £589; net health gain = −0.003 QALYs at the threshold of £15,000 per QALY gained per index family assessed). The uncertainties relate to the generalisability of the input data to the FH patients and FH services in the UK, hence the generalisability of the cost-effectiveness results, and the effect of cholesterol burden on CVD risk.

Acceptability of cascade-testing protocols for familial hypercholesterolaemia to patients and health professionals

The qualitative study in two UK settings with a purposeful sample of 40 index patients, relatives and health professionals found that a solely indirect contact approach was often problematic. A service-led direct-contact approach was more reliable and effective. Flexibly combining approaches (using either or both), guided by consultation with each index patient and tailored to differing relationships within families, may have greater acceptability and success to facilitate uptake of cascade testing. Experience related to quality of communication about FH, the accessibility and organisation of pathways, and continuity of care further determined acceptability of approach. A FH specialist nurse-led model providing adequate time for enhanced communication and continuity of care for families from commencement and throughout the cascade-testing pathway was preferred and strongly supported.

Conclusion

The analysis of PASS databases suggested that protocols that involved a more direct approach to relatives led to increased completion of cascade testing, with qualitative interviews supporting this service-led direct approach. In the related systematic review, limited evidence from four low-quality studies indicated that the combined approach (i.e. health professionals directly contacting some relatives and contacting others indirectly through index cases) may result in more relatives being tested than the direct approach. The flexibility offered by the combined approach was also attractive to patients interviewed in the study. Findings from the PASS analysis were at risk of bias given the observational nature of the data.

Epidemiological analysis of FH-coded patients in primary care databases informed treatment patterns, identifying that only one-quarter of individuals start treatment within 2 years, and, of those treated, only 30% reach LDL-C reduction levels recommended by NICE FH guidelines.

The primary care data set and the specialist FH (Simon Broome) register both confirmed that (long-term) CVD risk is greater among FH patients than among non-FH patients and the general population. This was both for overall risk and risk of specific CVD conditions (e.g. CHD, stroke, PVD). The FH register also demonstrated comparatively poorer outcomes among women and younger patients.

In the cost-effectiveness analysis, the cascade-testing protocols diagnosing the most relatives and providing the best value for money were those in which index cases were selected for genetic testing, based on current criteria used by Wales and Wessex FH services, and involved the FH service directly contacting relatives, and contacting the second-degree relatives even if their first-degree relative has not been tested. Focusing genetic testing on relatives not taking LLT and with LDL-C of around 2–6 mmol/l (depending on age), with diagnosis of other relatives based on LDL-C levels, is better value for money for the NHS than offering genetic testing to all.

Limitations

The systematic reviews on contact strategies identified a few low-quality studies and no relevant studies on diagnostic accuracy. These could not be used in the cost-effectiveness analysis. The CPRD primary care data set defined FH as patients coded with FH in primary care. We acknowledge that this may not be accurate. The major limitations of the cost-effectiveness analyses related to the assumptions required, namely about the generalisability of the available data to FH patients and FH services, about the effect of cholesterol burden on CVD risk and long-term CVD risk. Hence, there is uncertainty about the generalisability of the cost-effectiveness results to clinical practice. Furthermore, patient recruitment for interviews was limited to white English-speaking patients, and genetic counsellors were not available for interviews.

These findings are consistent with the NICE guideline recommendations. The further elaboration on the most effective protocol, specifically testing first-and second-degree relatives simultaneously, may be considered in future updates to the FH guidelines.

Research recommendations

- Establish a long-term FH cohort with robust measurement of cholesterol levels, treatment and cardiovascular outcomes.
- Conduct a randomised study directly comparing different approaches to contact relatives.
- Conduct qualitative interviews in a more diverse patient population, including ethnic minorities, males and more distant relatives.

Study registration

This study is registered as PROSPERO CRD42018117445 and CRD42019125775.

Funding

This project was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 27, No. 16. See the NIHR Journals Library website for further project information.

Health Technology Assessment

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 3.6

Launched in 1997, *Health Technology Assessment* (HTA) has an impact factor of 3.6 and is ranked 32nd (out of 105 titles) in the 'Health Care Sciences & Services' category of the Clarivate 2021 Journal Citation Reports (Science Edition). It is also indexed by MEDLINE, CINAHL (EBSCO Information Services, Ipswich, MA, USA), Embase (Elsevier, Amsterdam, the Netherlands), NCBI Bookshelf, DOAJ, Europe PMC, the Cochrane Library (John Wiley & Sons, Inc., Hoboken, NJ, USA), INAHTA, the British Nursing Index (ProQuest LLC, Ann Arbor, MI, USA), Ulrichsweb™ (ProQuest LLC, Ann Arbor, MI, USA) and the Science Citation Index Expanded™ (Clarivate™, Philadelphia, PA, USA).

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This report

The research reported in this issue of the journal was funded by the HTA programme as project number 15/134/02. The contractual start date was in April 2017. The draft report began editorial review in May 2021 and was accepted for publication in June 2022. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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