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Improving the identification of patients with a genetic diagnosis of familial hypercholesterolaemia in primary care: A strategy to achieve the NHS long term plan

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ABSTRACT

Background and aims: We aimed to validate a nurse-led process using electronic health records to identify those at risk of familial hypercholesterolaemia (FH) for genetic diagnosis in primary care.
Methods: Those at risk of FH were identified using searches developed and refined locally and implemented in primary care by a trained nurse; they were invited for further assessment and genetic testing if indicated. Family members at risk of FH were identified and invited for cascade testing.
Results: In total 94,444 patient records were screened (expected prevalence of FH (1 in 250); 377). Of 176 records which already had a diagnostic for FH, 15 had been genetically confirmed and one was undergoing DNA testing. A further 572 (0.61%) were identified as high risk of FH. After desktop screening, 113 (15%) were invited for further assessment. Of these, 73 individuals attended the primary care clinic (64%) of whom 61 (54%) underwent proband genetic testing. Pathogenic variants were detected in 22 cases (36%) and variants of unknown significance in a further 4 cases; a total of 26 probands (43%) were therefore referred for family cascade testing.
Conclusions: An optimised FH identification pathway, based on the NICE CG71 recommendations for systematic searching of primary care electronic health records, can be deployed successfully in primary care settings.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide, accounting for 31% of all global deaths [1]. An important under-diagnosed cause of premature CVD, specifically coronary heart disease (CHD), is familial hypercholesterolaemia (FH) [2,3]. FH is an inherited disease, characterised by lifelong high cholesterol levels – specifically low-density lipoprotein-cholesterol (LDL-C) [3]. Left untreated, male patients with FH have a 50% risk of developing CHD by the age of 50, and women a 30% risk by the age of 60 [4]. With an estimated prevalence of 1:200–250 [5,6], FH affects 34 million people worldwide [7]. As many as 250,000 people in the UK may be living with the condition, but it is estimated that only around 15,000 patients have a formal genetic diagnosis of FH [3,8].

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Improving the detection and treatment of high cholesterol and conditions such as FH that are associated with greatly increased cardiovascular risk is a strategic public health priority. Both Public Health England (PHE) and The NHS Long Term Plan have set targets to prevent 150,000 CVD events over the next 10 years by improving the detection and treatment of high-risk conditions including high cholesterol (hypercholesterolaemia) [1,9]. There is also a drive to expand access to genetic testing for FH to support the diagnosis and treatment of patients at genetic risk of sudden cardiac death [9]. According to current prevalence estimates, fewer than 7% of patients with FH in the UK are currently identified [10], but the NHS Long Term Plan aims to improve these diagnosis rates to at least 25% of FH patients in the next five years through the NHS genomics programme [9].

In the UK, NICE clinical guidelines (CG71, CG181) and quality standard (QS41) recommend healthcare professionals (HCPs) consider the possibility of FH in adults with raised cholesterol, especially in those with a personal or family history of premature CHD [2,11]. Once index cases have been identified, in most cases opportunistically, and the diagnosis of FH has been confirmed by genetic testing, cascade testing of at-risk family members can lead to early diagnosis of FH and substantial improvements in CVD outcomes. In 2017 NICE updated the Familial Hypercholesterolaemia guideline to recommend systematic searches of primary care records for people considered to be at highest risk of FH (CG71; 1.1.2; Total cholesterol $>$ 7.5 mmol/L in those aged $<$30 yrs and $>$9.0 mmol/L in those aged $\geq$30 yrs). However, despite these evidence-based recommendations, the recognised gap in CVD prevention in the UK and the potential opportunities to reduce morbidity and mortality, the NICE recommended clinical pathways are not established throughout England.

In previous audit studies in primary care [12,13] implementation of systematic electronic searches and targeted case note review markedly improved the rates of FH diagnosis based on clinical criteria but access to confirmatory genetic testing was not available and therefore subsequent family cascade testing could not be undertaken. We set out to build upon the lessons learned from these audits by developing a FH case finding and genetic testing pathway to assess the feasibility of a primary care based diagnostic strategy for FH within the footprint of the Academic Health Science Network for North East and North Cumbria (AHSN NENC). At the time of this study AHSN- NENC which encompassed a target patient population of approximately 3.5 million with (at the time of the study) 12 CCGs. The aims of the project were to proactively identify those at high risk of FH using an integrated, optimised FH search tool within GP IT systems and establishment of a nurse-led FH genetic testing outreach service.

2. Patients and methods

2.1. Setting up the programme

In order to achieve the maximum impact on FH diagnostic rates, the pilot project focussed on areas in the south of the AHSN-NENC because of historical poor access to lipid clinic services and lower rates of genetic testing. A dedicated FH nurse was appointed to coordinate the implementation of the pilot to triage, identify and assess patients for genetic testing for all phases of the project.

The project involved 9 practices who proactively volunteered to be involved in the project. These practices came from across the whole NENC geography but predominantly from the south of the region and were from both rural and urban areas. In total these practices included 94,444 patients. In this population we would anticipate 1 in 250 individuals would have FH [5,6] giving an expected 377 affected individuals. The project was reviewed by the local research department and considered to be a service development with an associated evaluation and therefore did not require research ethical approval.

2.2. Implementing the FH case-finding

An FH identification resource was developed to identify patients at high-risk of FH in primary care by searching electronic medical records in GP IT systems and generating a ranked FH risk score for each patient (Fig. 1). The service was implemented in two phases.

2.2.1. Phase 1 search

Initially, a system developed in collaboration with PRIMIS [14] at the University of Nottingham was used. Incorporating the FAMCAT algorithm, based on the Simon Broome diagnostic criteria, it identified clinical and laboratory data associated with FH from primary care records including highest total cholesterol, LDL cholesterol, triglyceride levels, previous history of CHD, family history of myocardial infarction (MI), previous FH diagnosis and elevated cholesterol levels [15]. Cases already coded as Familial Hypercholeserolaemia in the primary care record were reserved for a separate desktop review. After review of the outputs from the first 4 practices (population 45,123) with the steering group it became clear that the application of this system in the primary care record was classifying large numbers of cases as “very high risk of FH” (VHRFH), who on manual case note and/or face to face review who were not eligible for FH genetic testing according to local criteria (Dutch Lipid Clinic Network Score greater than 5), and that the search strategy required modification to increase specificity.

2.2.2. Phase 2 search

In order to improve the number of potentially eligible cases selected for manual case note and/or face to face reviews, a modified algorithm was developed in collaboration with the Clinical Digital Resource Collaborative (CDRC). Known as “CDRC Composite” this search strategy was based on a combination of:

- NICE CG71 guideline recommended total cholesterol thresholds for FH identification on primary care searches, modified to include corresponding raised LDL- and non-HDL cholesterol thresholds and with an adjustment based on fasting triglyceride levels to help exclude patients with other causes of hypercholesterolaemia [16].
- A virtual, estimated Dutch Lipid Clinic Network Score (DLCNS) based on information available in the primary care electronic record

The CDRC FH resource was accessible within the GP IT system (directly integrated into GP practices using SystmOne) and allowed health records to be screened in real-time and notes applied directly to the patient records (Fig. 2). As before, cases already coded as familial hypercholeserolaemia in the primary care record were reserved for a separate desktop review.

Finally, two alternative candidate FH search strategies (a CDRC calculated FAMCAT score and premature CHD before 50 years) were also made accessible within the GP IT system and allowed health records to be screened in parallel to identify any cases which might be missed by the “CDRC Composite” search (Phase 3).

2.3. FH nurse triage process

Patients identified as “very high risk of FH” (VHRFH) using the CDRC and/or PRIMIS algorithms were subsequently triaged in a desktop review. After exclusion of patients with hypercholesterolaemia due to other causes or who were otherwise unsuitable (e.g. no longer registered), potentially eligible patients were ranked using an estimated Dutch Lipid Clinic Network score. The FH nurse specialist then worked closely with the GP practice leads to invite suitable patients into a dedicated outreach FH clinic to inform them of the service, conduct a full clinical assessment and offer to undertake genetic testing if appropriate. (Fig. 2). All materials developed by the project team and approved by the Steering Group are available via the AHSN NENC website [https://www.ahsn-nenc.org.uk/what-we-do/improving-pop

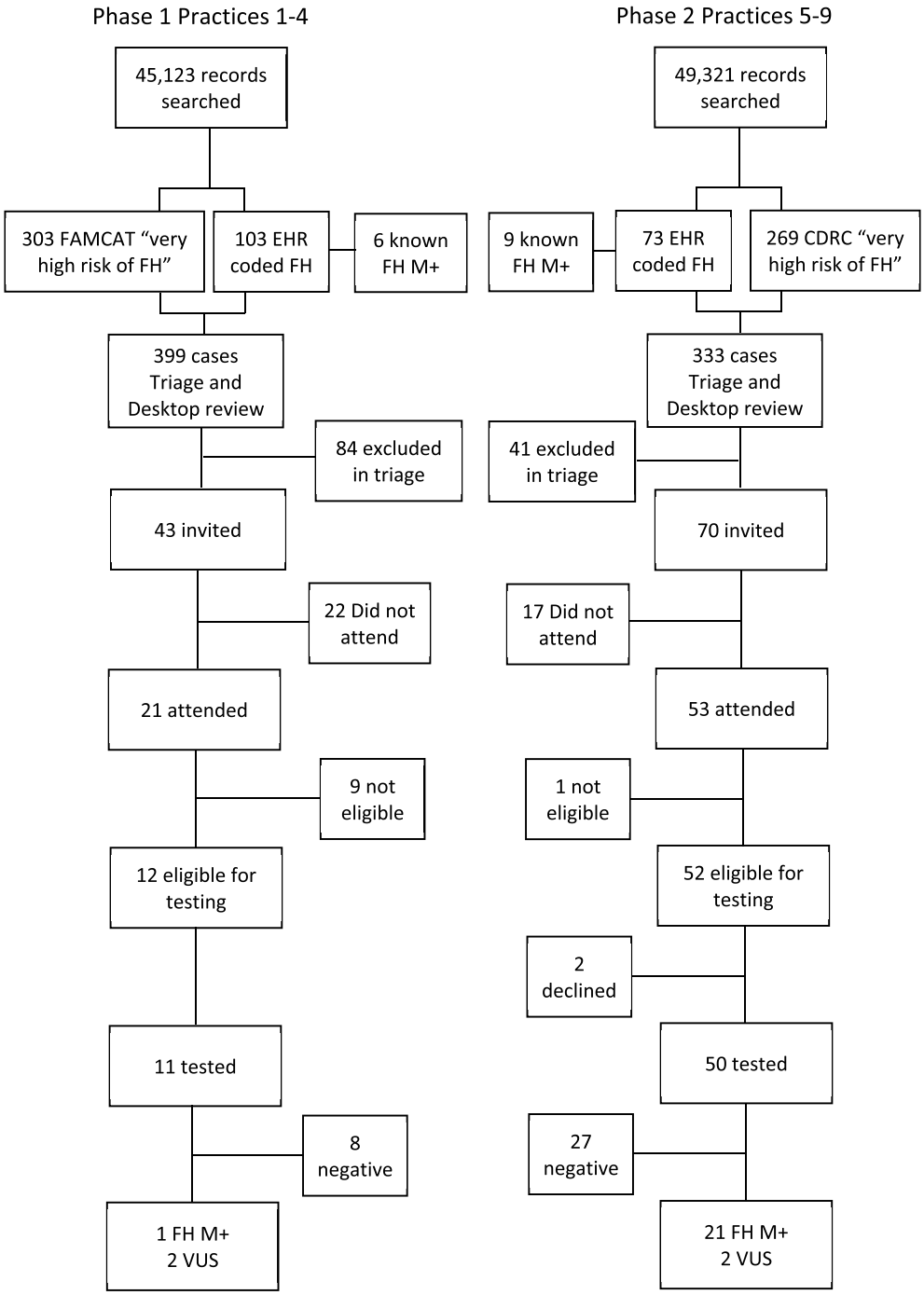

Fig. 1. FH case-finding service patient pathway.

ulation-health/familial-hypercholesterolaemia-fh/]. Where individuals were found to have a positive genetic test referral to a Specialist Lipid Service and separately to the Regional FH Cascade Service was made. Cascade testing has been offered to all those families where FH has been identified.

2.4. Laboratory procedures

For those who consented to genetic testing, blood samples were collected and sent to the Northern Genetics Service in Newcastle. DNA extracted from blood was subject to a two stage screening process. Samples were initially subject to a targeted assay testing for 22 pathogenic variants known to have a high prevalence within the North East and North Cumbria population. This short first stage test (SGT) was performed by MALDI-TOF mass array spectrometry (Agena) and data was analysed using MassARRAY Typer 4 software. In addition, genotype data from 12 SNPs associated with polygenic FH included in the SGT were used to calculate the 'polygenic SNP score' to determine the likelihood of monogenic/polygenic hypercholesterolaemia for each patient [17].

The full clinical details, laboratory data and family history of patients who tested negative for the targeted assay were reviewed in a multidisciplinary team meeting (MDT) before they were cleared to proceed for full pathogenic variant screening (FGT), including dosage analysis, in the *LDLR, PCSK9, APOE, APOB* and *LDLRAP1* genes by Next Generation Sequencing. Sequencing libraries were prepared using an Agilent

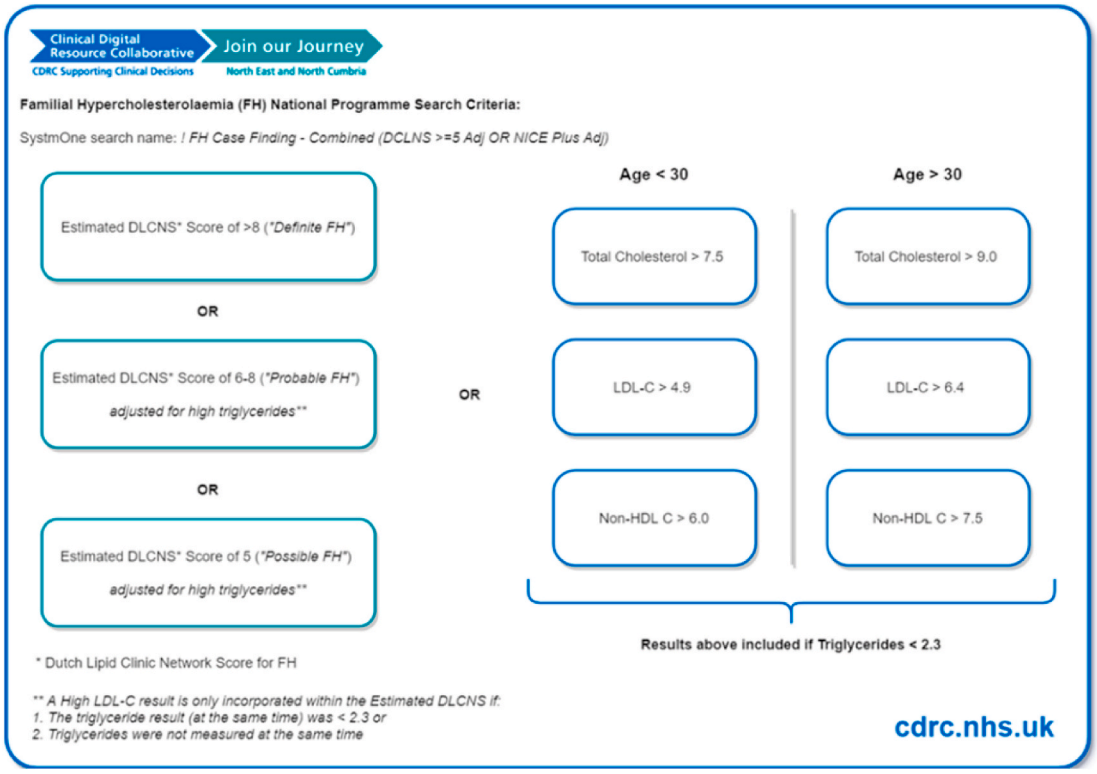

Fig. 2. Search criteria used to identify those at risk of familial hypercholesterolaemia using the Clinical Digital Resource Collaborative.

SureSelect hybridisation capture custom design reagent, sequenced using the Illumina NextSeq platform to a minimum read depth of 30x and data analysis performed using a bespoke bioinformatics pipeline. Coding exons, intron/exon boundaries for all genes and the 5' untranslated regions for *LDLR* and *PCSK9* were included in the analysis. Detected variants were assessed according to ACGS best practice guidelines (http://www.acgs.uk.com/) and reported accordingly.

In Phase 2 all patients were also offered Lipoprotein(a) testing (Roche Tinaquant Lipoprotein (a) Generation 2 assay on Roche Cobas Modular P, Roche Diagnostics GmbH).

2.5. Statistics and data analysis

A spreadsheet was used to calculate the Dutch score for each patient at desktop review. All data from the search results were entered to REDCap (Vanderbilt University) Version 10.6.4 and exported to a speadsheet to calculate the diagnostic yield for the individual searches.

If an index case was identified and screened at an outreach clinic in a GP practice and it became apparent, while taking a comprehensive family tree, that other individuals from the same search were in fact related to them, a single mutation test was performed for the variant already known in the family. However In order to fairly assess the accuracy and viability of the searches we made the supposition that each individual identified in the search was a potential index and all members of the family, not identified by cascade testing, were counted as indexes. It was assumed that 50% of first degree and 25% of second degree relatives of each unrelated proband would be carriers of the same pathogenic variant.

Lipid parameters among groups with and without pathogenic variants were compared using two-tailed Students T-test for 2 independent means at the significance level of 0.05.

3. Results

3.1. Phase 1 searches

The FAMCAT based PRIMIS FH audit tool was used across five GP practices. A total of 45,123 patient records were screened. Six patients were already known to have a genetic diagnosis of FH with one further patient undergoing genetic testing. A further 96 patients had a coded diagnosis of FH on the EHR. Three hundred and three (0.67%) additional patients were identified as being at very high-risk of FH (VHRFH). After exclusion of 84 patients with hypercholesterolaemia due to other causes or who were otherwise considered unsuitable on nurse-led desk top review of the patient records, 43 potentially eligible patients ranked highest with estimated Dutch Lipid Clinic Network score were invited for screening and 21 (49%) attended the outreach FH clinic. Of these, 12 (57%) were deemed eligible for genetic testing. Of 11 patients with completed tests, 8 patients received a negative result, Variants of Uncertain Significance (VUS) were identified (on FGT) in 2 patients and a pathogenic variant was identified in 1 patient (on SGT). The latter patient had in total 11 first degree and 18 s degree relatives, of whom we might expect to up to a further 10 FH positive patients on cascade testing.

Several implementation and operational challenges were identified using this initial approach which proved a barrier to routine adoption:

1). The PRIMIS tool used the hard drive in GP IT systems and was not integrated with the practice medical records system – this presented a security challenge when accessing all GP systems and was therefore impractical for HCPs to use.
2). The search schedule of the tool was limited to every 6 months and utilised the highest total cholesterol measurement recorded in the patient records, which may not be clinically relevant.
3). The criteria for ranking patients at very high and high-risk of FH did not exclude hypercholesterolaemia associated with

significant hypertriglyceridemia and did not identify those scoring highest on the estimated Dutch Lipid Clinic Network score.

In view of these concerns and the lower than expected yield of genetically confirmed cases we modified the search strategy for Phase 2 practices.

3.2. Phase 2 searches – the CDRC optimised pathway

CDRC FH resource was developed based on the experience gained in Phase 1 (see Methods). 49,321 patient records were reviewed from 5 practices. Nine patients were identified who already had a genetic diagnosis of FH. A further 64 patients had a coded diagnosis of FH on the EHR. 269 (0.55%) additional patients were identified as being at high risk of FH. After exclusion of 41 patients with hypercholesterolaemia due to other causes or who were otherwise unsuitable on nurse-led desk top review of the patient records, 70 potentially eligible patients ranked highest with estimated Dutch Lipid Clinic Network score were invited for screening (21%). Of these 53 individuals attended the clinic (76%) of whom 52 (74%) were eligible for testing; two patients declined to be involved. Of 50 patients tested, 26 patients received a negative result. Variants of Uncertain Significance (VUS) were identified (on FGS) in 2 patients and a pathogenic variant was identified in 21 patients (16 patients on SGT; 5 on FGS), with ages ranging from 27 to 89 years. An additional patient, flagged in Phase 3 by one of alternative candidate FH search strategies (CDRC calculated FAMCAT), met the Simon Broome criteria based on a single LDL-C measurement recorded after MI aged 50, but was not flagged by the CDRC optimised search criteria and therefore excluded from the CDRC composite analysis. However, he was considered eligible for genetic testing and was subsequently found to have a common pathogenic mutation in the *APOB* gene. After exclusion of this patient and taking account of those indexes subsequently shown to be related, in Phase 2 we had 16 at risk families with 43 first degree and 71 s degree relatives, of whom we might expect to find a further 39 FH positive patients on cascade testing, however based on the typical cascade yield in FH services across England (1.2 per proband) at least 19 FH cascade diagnoses are anticipated, bringing the total diagnosed in this population to 50, or just over 25% of the expected 197 cases predicted.

3.3. Phase 1 and 2 searches combined results

In total (Phases 1 and 2 combined) 572 people (0.61%) were identified as being at high risk of FH in addition to 176 already coded as FH in the EHR. 114 (15%) were invited for further assessment, including 11% of the Phase 1 search group and 21% of the Phase 2 search group. Of these, 74 individuals attended the clinic (65%) of whom 64 (86%) were eligible for testing. In 61 patients (84%) in whom genetic testing was performed, a pathogenic variant was identified in 22 patients (36%) (Table 1). The results of Phase 1 and Phase 2 are summarised in the flow chart (Fig. 3). Therefore, 0.028% of the total population, 3.6% of those identified as high risk and 43% of those who underwent a FH genetic test were found to have a genetic variant confirming or suggestive of FH. The genetic variants identified are shown in Supplementary Table 1. When the lipid profiles were compared, those with a pathogenic variant (MPos) had significantly higher LDL-Cholesterol than those with no pathogenic variant detected (MNeg) (MPos n = 20 with result available; mean LDL-C 7.49 mmol/L, MNeg n = 35; mean LDL-C 6.38 mmol/L; $p = 0.006$), however Total cholesterol (MPos n = 26; mean Total-C 9.48 mmol/L, MNeg n = 35; mean Total-C 8.83 mmol/L; $p = 0.103$) and Triglycerides (MPos n = 26; mean Triglycerides 1.62 mmol/L, MNeg n = 35; mean Triglycerides 1.91 mmol/L; $p = 0.059$) were not significantly different. The clinical and laboratory data of patients with positive and negative genetic test results are presented in Supplementary Tables S1 and S2.

4. Discussion

We have developed an optimised primary care identification pathway for FH based on a modified version of the NICE CG71 recommendation for systematic searches of primary care records combined with an estimated DLCNS (Fig. 2). We have shown that this strategy, guiding confirmatory genetic testing of index cases and cascade testing of at-risk relatives can be deployed successfully in primary care. By searching electronic patient records using algorithms based upon existing screening recommendations and scoring systems we were able to detect those patients most appropriate for genetic testing, at least matching the diagnostic yield seen in secondary care settings. Direct access to genetic testing in a primary care setting, when performed by an appropriately trained nurse, efficiently detects those with monogenic FH allowing initiation of treatment and cascade testing of at-risk relatives reducing the burden on local lipid services.

In the first phase of implementation there was a low attendance for further assessment with the FH nurse. Using improved patient information developed in partnership with patient groups we have been able ensure that high numbers of those invited for genetic testing are more likely to attend. Working in partnership with the practice team to deploy telephone invitations to discuss the pathway also enhanced patient engagement.

It is important to emphasise that for every FH patient diagnosed there will be other members of their family with undiagnosed FH, so it is vital to begin pro-actively identifying FH patients to reduce the potential number of CV events caused by untreated FH. As expected, our study found that in many of the individuals identified with FH, there were significant numbers of first and second-degree relatives who should undergo cascade testing for identified variants associated with FH and further cardiovascular risk assessment. We would expect 50% of first degree and 25% of second-degree relatives to test positive for FH, however in England the uptake of cascade testing from genetically confirmed FH positive probands is low at approximately 2.4 relatives tested per proband and 1.2 testing positive, on average. The potential for cascade testing among the relatives of our patients appears higher, and however negative attitudes to cascade testing [18] mean that relatives are often reluctant to come forward. We plan to undertake cascade testing in the local community setting where possible, which we hope may improve family engagement.

The key challenge for successfully implementing the FH case finding service in the primary care setting was ensuring that only the most appropriate patients were identified, requiring searches with a high specificity, at the expense of sensitivity, as intended in the NICE recommendations. This improves efficiency and ensures that per practice the workload is manageable and realistic. A more proactive approach to data collection into the primary care electronic patient record regarding

Table 1
Total numbers of individuals at each stage of the process for each search type and for the total project. N (%).

	Population size	Patients identified as high risk by algorithm	Patients invited for appointment following desktop review	Patients undergoing FH genetic testing	Positive cases
PRIMIS	45,123	303 (0.67)	43 (14)	12 (27)	3 (23)
CDRC	49,321	269 (0.54)	71 (27)	51 (73)	24 (47)
TOTAL	**94,444**	**572 (0.61)**	**114 (20)**	**63 (55)**	**27 (43)**

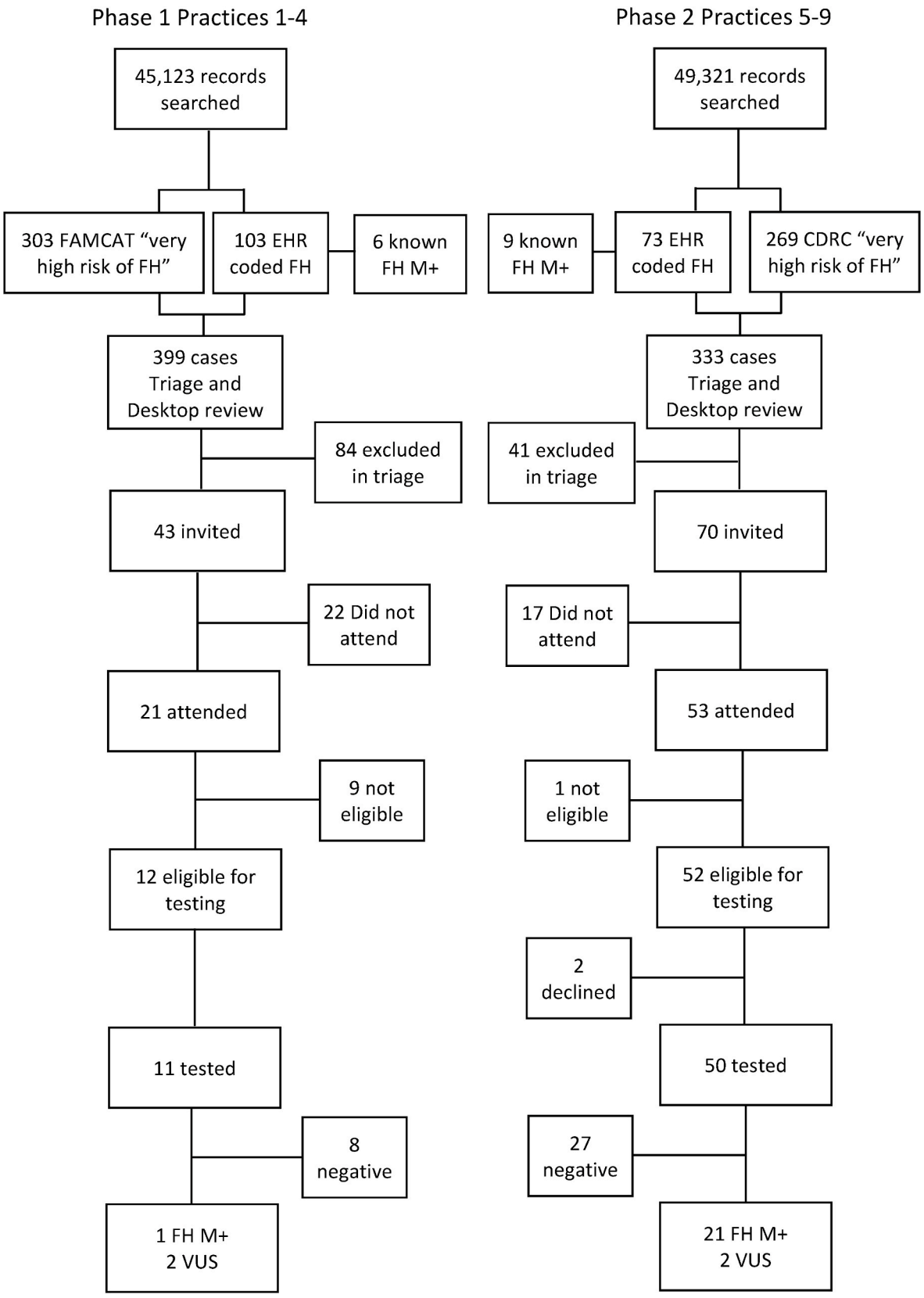

Fig. 3. Flow chart summarizing the results of Phase 1 and Phase 2.

family history and documentation of other personal and family cardiac risk factors will further improve the efficiency and effectiveness of identifying appropriate patients. We believe our bespoke resources together with a refined triage based on the NICE CG71 Guidelines [2] optimises the pathway. These resources, developed for SystmONE in the first instance and, following modification, will also be available for use on EMIS systems (the two systems most widely used in the UK) and are available free for use (cdrc.nhs.uk).

Each patient identified was triaged and an accurate family history for CVD and FH risk factors obtained. This could be time consuming if a large number of inappropriate patients are identified and has capacity and logistical implications for both the patient and practitioner. This is important when considering scaling up the service, planning workforce requirements and the overall UK ambition to achieve the NHS LTP ambition for FH detection.

Equally, it is important to ensure a full and detailed history of first, second and, where possible, third degree relatives is obtained. In our study a decision was made by Steering Committee to classify all individuals identified in primary care searches as index cases as it was felt not possible to identify family groups from the primary care records in a time efficient manner during the pilot project. During the second phase of the project an index case was identified and screened at a GP practice and it was whilst taking a comprehensive family tree that other individuals from the same search were found to be related to them. Moreover by checking family records against family trees of known individuals with genetic diagnoses we were able to identify that they were related to an index (a maternal cousin) who was tested more than twenty years previously [19] but who had never had family cascade testing beyond immediate family. This new index was tested for the known gene in the family and the result was positive. However using the supposition of each individual identified in the searches being an index and wishing to ensure the accuracy and viability of the searches all six members of the same family are included as indexes. Taking time to review the pedigree of patients selected for genetic testing may identify a common ancestry and allow genetic testing to be done more efficiently and in a less expensive manner by undertaking full gene sequencing only on a single proband and subsequent cascade testing of all known relatives.

A high proportion of positive patients (18 out of 23) were identified via the short genetic test utilised across the AHSN-NENC footprint. This targeted approach may have economic advantages when considering more widespread FH genetic testing in Primary care populations where the common mutation spectrum is already known as the short genetic (genotyping) test is considerably cheaper that full genetic sequencing. However, this approach may not be suitable for other areas particularly if they have high levels of diversity. Also it is crucial to highlight the 2 step approach we have used still relies on undertaking full genetic sequencing on patients who test negative for the short test, and this has led to the identification of 4 index cases with VUS which will need further evaluation by family segregation studies in the first instance.

Critical to the success of initiating, implementing and evaluating the FH case-finding service was the collaborative engagement and effective communication between multiple stakeholder groups and individuals. Advocacy, collaboration and commitment from GPs, CCGs and patients, with a dedicated workforce to triage patient records and manage the genetic testing clinics was key to the success of the service.

Historically, patients identified opportunistically have been referred to secondary care Lipid clinics to ascertain whether or not they could have Familial Hypercholesterolaemia. Patients tend to be referred opportunistically and may not be considered for FH genetic testing even if they do fulfil the recognised diagnostic (Simon Broome) criteria. To avoid wasting limited genetic testing resources, further labour intensive and time-consuming work is often required to identify a more severely affected relative who is a better target for proband genetic testing, but this is often not possible as many, particularly in rural populations, may decline invitations to attend secondary care services. It is clear that now primary care can play its part [20,21] by implementing a systematic targeted approach within to identify patients who are eligible, capable of achieving a diagnostic yield comparable to secondary care clinics, can both improve the identification and treatment of patients with FH and increase capacity in Lipid clinics and thereby contribute to achieving the UK NHS LTP ambition. The integration electronic searches such as CDRC into primary care systems will allow opportunistic identification of those with FH but also can facilitate population-based approaches. Searches can be done to identify those at increased risk, and dedicated clinics performed to address those at risk. Most of this can be done remotely potentially using video consultation in order to optimise efficiency. The CDRC searches can be modified to reduce/increase sensitivity/specificity and these approaches could be tested in an ever-improved QI process. Based on insights gained in the current project, the inclusion of age specific lipid thresholds may improve the identification of younger FH patients who are under-represented among those detected with the current searches and diagnostic criteria applying fixed LDL-cholesterol thresholds.

Our strategy is successful at detecting those with FH where accurate and comprehensive patient information is held on the electronic health care records and the search criteria are targeted to reflect nationally adopted evidence based guidelines for FH diagnosis. As such our strategy may only be applicable in healthcare systems where similar, routinely recorded data are held in electronic records systems and are amenable to analysis in relation to locally agreed diagnostic guidelines.

Additional work is required to develop pathways for managing patients who were identified as being at high risk of FH but were either ineligible for genetic testing or did not attend the screening clinic. Some of these patients will have FH but other factors such a polygenic hypercholesterolaemia and high levels of Lipoprotein (a) may also be contributing to an apparent FH phenotype [15,16]. Collaborative work between Primary and Secondary care could lead to a process of further risk stratification to determine which individuals should be referred on to the Lipid clinic for further assessment.

4.1. Conclusions

This study highlights the feasibility and process involved in implementing a service in primary care that identifies patients at high risk of FH. It represents an opportunity to improve FH diagnostic rates and is a strategy to meet the targets set by Public Health England and the NHS Long-Term Plan to identify at least 25% of those with FH by 2024 in order to substantially reduce the incidence of CVD and premature mortality in these high risk patients. However, our study has also shown that this is just the beginning in terms of opportunities to optimise lipid management. Our approach will take steps towards the UK NHS Long Term Plan target, however, that remains a long way from identifying and managing all of those with FH and exploring potential refinements to our pathway and cascade testing strategies remain important priorites.

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CRediT authorship contribution statement

Lorna Ingoe: delivery of the project, development of the protocol, collation of the data. **Aimee Potter:** delivery of the project, development of the protocol, collation of the data. **Susan Musson:** delivery of the project, development of the protocol, collation of the data. **Dermot Neely:** Secondary care lipid expert; developed initial proposal, member

of the steering group; oversight of delivery of the project, development of the CDRC searches, final analysis and interpretation. **Guy Pilkington:** Primary care lipid expert; developed initial proposal; member of the steering group; final analysis and interpretation. **A. Joy Allen:** methodological development of the project; developed initial proposal; member of the steering group; final analysis and interpretation. **Danielle Reay:** development of the genetic analyses, interpretation and analysis. **Ahai Luvai:** Secondary care lipid expert; lipoprotein analysis and interpretation. **Ciaron McAnulty:** development of the genetic analyses, interpretation and analysis. **Nick Camm:** development of the genetic analyses, interpretation and analysis. **Ian Berry:** development of the genetic analyses, interpretation and analysis. **Jody Nichols:** development and delivery of the CDRC searches. **Gareth Forbes:** development and delivery of the CDRC searches. **Julia Newton:** development of the project and overall delivery; completed first draft of the manuscript. **Peter E. Carey:** Secondary care lipid expert; developed initial proposal, chair of the steering group; oversight of delivery of the project; development of the CDRC searches; final analysis and interpretation. All authors have reviewed and approved the final drafts of the manuscript.

Author contributions

LI, AP, SM: delivery of the project, development of the protocol, collation of the data. DN: Secondary care lipid expert; developed initial proposal, member of the steering group; oversight of delivery of the project, development of the CDRC searches, final analysis and interpretation. GP: Primary care lipid expert; developed initial proposal; member of the steering group; final analysis and interpretation. JA: methodological development of the project; developed initial proposal; member of the steering group; final analysis and interpretation. AL: Secondary care lipid expert; lipoprotein analysis and interpretation. DR, CM,NC, IB: development of the genetic analyses, interpretation and analysis. JNi & GF: development and delivery of the CDRC searches. JN: development of the project and overall delivery; completed first draft of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2021.03.035.

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