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Screening for familial hypercholesterolaemia in primary care - time for general practice to play its part

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Abstract

Fifty per cent of first-degree relatives of index cases with familial hypercholesterolemia (FH) inherit the disorder. Despite cascade screening being the most cost-effective method for detecting new cases, only a minority of individuals with FH are currently identified. Primary care is a key target area to increase identification of new index cases and initiate cascade screening, thereby finding close relatives of all probands. Increasing public and health professional awareness about FH is essential.

In the United Kingdom and in Australia, most of the population are reviewed by a General Practitioner (GP) at least once over a three-year period, offering opportunities to check for FH as part of routine clinical consultations. Such opportunistic approaches can be supplemented by systematically searching electronic health records with information technology tools that identify high risk patients. GPs can help investigate and implement results of this data retrieval.

Current evidence suggests that early detection of FH and cascade testing meet most of the criteria for a worthwhile screening program. Among heterozygous patients the long latent period before the expected onset of coronary artery disease provides an opportunity for initiating effective drug and lifestyle changes. The greatest challenge for primary care is to implement an efficacious model of care that incorporates sustainable identification and management pathways.

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Introduction

There is a general lack of public[1-3] and health professional[4-7] awareness of heterozygous Familial hypercholesterolaemia (FH) as a common, autosomal dominant disorder of lipid metabolism[8-10]. FH can cause premature coronary artery disease (CAD) if left untreated[11] with up to 50% of males likely to develop CAD by age 50 years and 30% of females similarly affected by age 60 years. Owing to a genetic defect in the low-density lipoprotein (LDL)-receptor pathway, affected patients cannot clear LDL particles from the circulation, which untreated leads to life-long, accumulation of low-density lipoprotein cholesterol (LDL-c) in plasma and accelerated atherosclerosis[8, 10, 12, 13]. FH patients cannot be managed solely by diet and lifestyle modifications. The cumulative cholesterol burden in homozygous FH is much greater as the condition is inherited from both parents[8]. Such patients develop severe life-threatening coronary heart disease (CHD) and other vascular complications in late childhood and adolescence if not recognised and treated.

FH affects 1 in 250 of the population[14-16]. Such a prevalence would expect to yield over 30 million patients worldwide, 240,000 in the United Kingdom (UK) and 90,000 in Australia. With over 85% of the Australian and UK population attending a General Practitioner (GP) at least once a year[17-19], opportunities exist for primary care to play a much more active role in the detection and care of FH patients in the future.

Despite increasing knowledge of the clinical hallmarks of FH – elevated LDL-c levels, family and personal history of premature coronary heart disease, premature arcus cornealis and tendon xanthomata, most cases of FH are still not being recognised[1, 9, 12]. Amongst patients recognised as having FH, most remain under-treated[9]. Various explanations have been offered to explain these missed opportunities for diagnoses

including busy clinical settings at tertiary and primary care level, pressure on bed availability and early discharge policies from hospitals.[20] Increasing complexity and amount of multimorbidity[21] in routine clinical presentations to GPs make recognition of FH especially challenging[22].

Coronary care units are other settings where FH may be identified. Patients with early onset of symptoms of ischemic heart disease may be admitted for further assessment and treatment. Such encounters will usually involve a shared care role for GPs, cardiologist and hospital specialist. Evidence to date suggests these are often missed opportunities for FH diagnoses in some patients[20].

Effective treatment is available and earlier beliefs that regression of atheromatous plaques could not be achieved are being challenged with studies showing intensive drug therapy can have a beneficial effect[23, 24]. Compliance with optimum treatment, usually statins, can be problematic at both patient and health professional levels[12, 25] and needs regular review and re-enforcement.

We review the potential to increase the role of primary care in the detection and care of FH.

International guidelines and approaches

The Consensus Statement of the European Atherosclerosis Society[9] and the International FH Foundation[26] both recommend that most patients with FH should be managed in the primary care setting and preferably in the family context. They advise that there should be provision for more complex cases, including children, to be managed through specialist lipid or FH clinics.

It is increasingly recognised that childhood and early adolescence offer the most favourable timeframe for diagnosing FH as well as introducing and maintaining

lifelong treatment and management strategies[3, 9, 12]. To achieve such radical care from a young age will require a shift in community and health professional perceptions of FH and its effects on the young. Little attention has been given to date to screening for FH in general practice where most affected patients are found.

In countries with a history of dedicated screening programs, such as the Netherlands and Norway, the outcomes in terms of newly diagnosed FH index cases and cascade tested relatives are much higher than countries lacking any formal screening program (usually <1%)[9, 27].

Evidence suggests that cascade screening of close relatives is generally highly acceptable and does not impact on quality of life[27]. The Dutch FH cascade screening program operated between 1994 and 2014 using the services of genetic field workers and was very successful[27]. Since the program was modified due to changes in the Dutch Health System, numbers diagnosed have dropped[27].

Most Australian and UK primary care practices are fully computerised, often with links to pathology providers and hospital services, thus lending themselves to electronic examination of patient databases for chronic hereditary conditions such as FH. In Australia, laboratory alerts either through a direct telephone call[28] from the chemical pathologist to GP or through flagging of raised lipids reports raising possibility of FH[29, 30] have been successful. Other Australian community-based initiatives include examining general practice and laboratory databases[31], use of algorithm[32] or data extractions tools[33].

In the UK, the accessibility to most GPs of regionally located specialist lipid clinics has provided valuable additional support for primary care management[34] while GP-based approaches involving database searches have also been trialled[35, 36].

In Slovenia, the use of universal screening for children aged over 5 years has been introduced to help with the detection of FH[37], but the practicalities and cost-effectiveness remain to be confirmed. In the United States, universal screening of cholesterol at age 9 to 11 has been endorsed by the American Academy of Pediatrics and the National Lipid Association (NLA), but has been incompletely undertaken and cost benefit analyses of this approach have not been performed[65].

Screening for FH in primary care

Primary care based screening for FH fulfils many of the revised Wilson and Jungner criteria[38], including the updated Australian Government population screening guidelines[39] (See **Table 1**)

Advances in approaches to screening in primary care

Primary care can make a more substantial contribution to the detection and care of FH[33, 36, 40]. Tests to help diagnose FH are simple and acceptable to the public, the available treatment is effective and case finding can take place in clinical practice[12].

The latent period between potential diagnosis of FH (preferably in childhood or adolescence) and the onset of CHD (early middle age) is in theory sufficient to allow effective, lifelong treatment to be instituted before atheromatous plaque development occurs. This time-frame is critical to facilitate an improved primary care role in FH recognition[12].

Research on strategies to identify FH in primary care:

1. Child-parent screening / Reverse cascade screening

Wald et al.[40] examined the efficacy and feasibility of child-parent screening for FH in primary care practices. They undertook the screening at routine immunisation

attendances by children aged 1 – 2 years at 92 general medical practices in the United Kingdom over a three-year period. A total of 84% of parents agreed to the heel-stick capillary blood sampling offered to test for FH. The child provided the screening entry point at an age identified as the most discriminatory for the measurement of cholesterol[41]. Once the child is identified as having FH, one of the parents will also harbour the condition enabling two generations to be effectively screened as part of the process.

For the 10,000 children screened, based on cholesterol levels, 40 children and 40 parents were identified as positive for FH, at high risk for cardiovascular disease (CVD) and offered appropriate treatments[40]. The population prevalence of children found to have FH was 1 in 270. A total of 32 of the 40 children screening positive for FH were found to have a genetic mutation while 8 did not. Child-parent screening was seen as a simple, effective and practical method to examine a population for the presence of FH[40].

2. Systematic and opportunistic screening and case finding in general practice

Primary care can significantly improve the identification and management of FH in the general population[3, 9, 12, 31] where the prevalence is about twice that previously estimated[14-16, 26]. A prevalence of 1 in 250 would yield 40 individuals with FH in a practice population of 10,000 patients. Most practices of this size would not realise this potential at risk group exists. For primary care to improve FH detection, greater health professional awareness of the significance of markedly elevated cholesterol levels in high risk patients, a family or personal history of premature CAD or death plus recognition of other tell-tale stigmata of FH, will be necessary[1, 3].

Extra workloads

Opportunities to increase detection of FH in general practice are becoming more sophisticated. New data extraction tools employing algorithms of the phenotypic features of FH (Dutch Lipid Clinic Network (DLCN)[42], Make Early Diagnosis to Prevent Early Deaths (MEDPED)[43] and Simon-Broome (S-B) criteria[44]) can minimise practice workloads while still focussing attention on detecting high risk patients.

In Australia, there have been attempts at improving detection and management of FH in the primary care sector[33, 45-47]. Models of care, which in the past have focussed on tertiary level hospital lipid clinics[3], are now looking at a greater involvement from primary care especially for patients without additional risk factors[22, 41].

Phenotypic v genetic testing

The DLCN criteria (DLCNC) score[42] is the preferred tool in Australia to help with phenotypic diagnosis of FH[26]. Cost, geographic and migration factors, plus lack of population density across most of the continent, are major handicaps towards use of genetic testing for all suspected FH patients[22]. The same barriers also preclude the widespread use of dedicated field workers[27] to undertake systematic contact tracing of close relatives. A more pragmatic approach involving use of the DLCNC score in the primary care setting is currently being trialled in Australia[47].

The use of genetic testing in the UK compared with the phenotypic approach advocated in Australia and in the United States offers an interesting comparison[34]. Current National Institute for Health and Care Excellence (NICE) guidelines[17] favour the critical importance of genetic testing to confirm monogenic FH. Only patients testing positive to the FH gene mutation will be given the diagnosis of FH. Other patients with the clinical features of FH (phenotypic) but no established mutation will

be designated as ‘polygenic hypercholesterolemia’. NICE guidelines[17] also advocate that only relatives of genetically positive index cases should be offered genetic testing to establish mutation positive FH. The obvious downside is that with over 1700 known FH mutations[48], not all are amenable to genetic testing and up to 40% may be missed[9].

National Institute for Health and Care Excellence (NICE) guidelines

In UK, the original NICE Guideline CG71[17] advised suspicion of FH diagnosis in adult if raised total cholesterol (> 7.5 mmol/l) especially with personal or family history of premature CHD. GPs should exclude secondary causes of FH, undertake detailed family history that is regularly updated and undertake thorough clinical examination to check for signs of elevated cholesterol, such as, tendon xanthomata[34]. Patients with ’definite’ or ‘possible’ FH on S-B criteria should be referred to specialist with FH expertise to confirm diagnosis, advise on management and help with co-ordination of cascade testing among close relatives. Many patients identified as ‘possible’ FH will not be confirmed as having the condition[49]. The 2017 NICE guidelines advise systematic searches of patient records for cholesterol over 9mmol/l as these have over 25% chance of having FH[17].

The absence of suitable infrastructure in primary care to assist with cascade testing of relatives is a major handicap[2]. Serious deficiencies have been found in patient knowledge about FH, their risk of a major cardiac event and the mode of inheritance across generations[50].

General practice search strategies

Gray et al.[35] undertook computer-based searches to look for likely FH patients at a primary care centre of 12,000 patients in South London. A total of 402 individual

patients were identified for review. After record review and using the DLCNC score[42], they identified 12 patients who scored 8 and above ('definite' FH); eight who score between 6 and 8 ('probable' FH) and a further 47 patients who scored between 3 and 5 ('possible' FH). Thus, a total of 20 patients met the criteria for 'definite' or 'probable' FH in the study. No cases with tendon xanthomata were found.

All patients with FH were noted to have early CAD and the authors concluded this finding as the key to reaching a diagnosis of FH. Commencement of treatment for elevated lipids with statins was noted to occur without the potential for FH being the key diagnosis being considered. This lost opportunity to screen close family members for the condition could have contributed to avoidable mortality in the circumstances[35].

The time factor involved was a limiting factor. Each manual search of medical records took about 30 minutes and amounted to 201 hours of additional work to examine the records of the 402 patients identified as being at higher risk[35]. The use of electronic screening tools combined with efficient clinical follow-up by GP and/or PN can offer a more time- and cost-effective systematic approach to identify FH patients in the primary care setting.

Familial Hypercholesterolaemia Case Ascertainment Tool (FAMCAT)

To improve and simplify identification of FH in British primary care electronic health records, a case ascertainment tool - Familial Hypercholesterolaemia Case Ascertainment Tool (FAMCAT)[36] was developed to identify those with the highest probability of the condition, with predictive accuracy (AUC) of 86%. FAMCAT allows more efficient use of limited resources by identifying those that need further clinical assessment, undergo referral for diagnosis and commencement of appropriate

preventative care for the future. Because patient health data is generally well recorded in the electronic medical records in general practices, FAMCAT uses coded variables to enhance the discriminatory information to identify the highest risk patients for further evaluation. This has been integrated into a national quality improvement tool[51].

TARB-Ex

In Australia, TARB-Ex[33] is an electronic research screening tool that uses information from regular general practice databases to identify patients with high DLCN scores who are then invited to attend the practice for further clinical investigation and phenotypic diagnosis. It was developed using Structured Query language (SQL) technology and integrated into Best Practice clinical software[52]. It has the capacity to be adapted for other SQL-based practice software including Medical Director, ZedMed, MedTech, Practix and Monet which taken together account over 90% of clinical software in Australia.

The performance of TARB-Ex was evaluated against a manual assessment by a GP of a subset of patients attending the practice[33]. Overall, results suggested that TARB-Ex was a fast and effective method for systematically identifying patients attending the practice with potential high risk of FH to enable further clinical investigation. Additional costs to the practice in terms of manpower and GP workload were minimised. TARB-Ex showed high sensitivity, specificity and negative predictive power, comparing favourably with manual review in just a fraction of the time – 10 minutes v 60 hours for manual review[33].

TARB-Ex integrates well into regular clinical practice. A GP, Practice Nurse (PN) or Practice Manager can undertake the initial screening process prior to recall for

clinical review. GP and PN involvement is limited to reviewing medical records of patients identified by TARB-Ex with high DLCNC scores and at risk for FH, exclude confounding secondary causes and decide which patients merit recall for clinical review.

Limitations of screening tools

All electronic screening tools are only as effective as the quality of the medical and blood pathology information stored in practice databases. The experience in UK and Australia shows family histories are poorly recorded for many patients[53-57] and is an acknowledged limitation of GP-based databases in comparison with hospital-based admissions and discharge summaries.

3. Community pathology alerts to GPs

Attempts have been made to link the performance of community pathology laboratories and general practice databases[29, 31] to help identify patients with specific indicators suggestive of FH and facilitate clinical follow-up. Evidence shows that a telephone call or alerting message from a chemical pathologist to the GP could have a powerful impact on whether an elevated cholesterol level was better investigated[28]. With GPs requesting over 90% of LDL-c levels in Australia, the opportunity for more innovative screening at the primary care level could be improved[29, 30].

The combination of greater reductions to target LDL-c levels and better use of specialist services could facilitate improvements in FH recognition and care. The shared care approach with GP management for lower to intermediate risk patients and specialist support for higher risk and more complex cases should be a logical development in care strategy.

4. Use of health checks

FH is ideally suited to use of periodic health checks and subsequent care plan management as part of a strategic approach to manage this chronic disease in general practice. Much emphasis with FH to date has focussed on 'top-down' approaches with identification and management primarily in tertiary hospital clinics and specialist care. In the early, asymptomatic phase of FH, early diagnosis and appropriate diet, lifestyle and drug interventions can be provided at the primary care level. Easy access to primary care services and regular follow-up checks at local practices can be provided. In Australia, care plans and 45-49 year-old health checks[58] developed by GPs and PNs, can be supported by other health professionals including dieticians, exercise physiologists and clinical psychologists while cardiologists, lipid specialists, endocrinologists and paediatricians can also contribute as required.

Many care plans have traditionally been viewed as mainly targeting the degenerative processes associated with ageing, diabetes, ischemic heart disease and strokes. FH can legitimately be added as a chronic lifelong condition that is well suited to a planned approach and management in primary care. Specialist help should always be available for more complex and difficult to manage patients and children.

In the UK, the 40 – 74 year-old age group health checks[58, 59] for patients with no recorded chronic health condition could be utilised to assess for FH risk. Patients with total cholesterol levels above 7.5mmol/l, should be targeted by GPs to undertake further investigations[34, 60].

5. Improve public awareness of FH

Improving public awareness of the possibility of FH, especially in the community setting, needs to be addressed[3, 50]. Many families may be aware of premature CVD

deaths in their own households but the significance of these past events and the potential future risk to their own health is often not fully grasped. Young off-spring of affected patients are likely to feel entirely healthy and lacking in symptoms and see no reason to commence life-long treatment for a condition they perceive as posing no immediate or potential threat. It may take on some relevance when a friend or colleague develops a life-threatening heart attack at a young age and their own potential risk is suddenly brought into sharper focus[22]. High risk patients with potential FH or known FH patients who refuse or are non-compliant with best practice medications and lifestyle modifications, should be offered an 'open door' approach to be seen early if they change their mind re future treatments.

6. Improve health professional awareness of FH

Despite increasing knowledge about the prevalence and risks of FH, many health professionals do not make a connection between FH and the patient's presenting condition[3, 6, 50]. A better appreciation of the underlying genetic nature of the disease[10, 13, 61] and the fact that it will not be solely responsive to dietary and lifestyle intervention is needed.

The current best management approach is through use of high intensity statins from a young age[1, 9, 11, 12, 14, 26, 62]. The lifetime increased accumulation of LDL-c means that the relative risk from FH makes the use of absolute CVD risk calculators[63] inappropriate in patients with FH and they should not be used[1, 9, 11, 14, 26]. Compliance with lifetime statin therapy may be a significant problem especially if family perceptions of such treatment is an issue[12]. GPs can play a major role in this area.

7. Improve support in primary care for cascade screening of close relatives of index cases

Cascade screening of close family relatives of known index cases is recognised as the most efficient and cost-effective approach for identifying new FH patients[3, 9, 64-66]. The evidence to support cascade testing of relatives is based on specialist centre approaches rather than screening from primary care[3]. The UK National Health Service (NHS) has recognised the difficulties posed by a lack of suitable infrastructure in primary care to undertake systematic cascade screening, and recommend that it should be undertaken through specialist centres instead[17, 34].

Evidence from the Netherlands showed the success of using genetic field workers to target close relatives of new index cases in a systematic fashion[27, 67]. The Dutch FH program which sought to find all FH patients, was centrally controlled and involved all specialists in cardiovascular care as well as all GPs, and had extensive media and scientific journal exposure to increase awareness at the general population and health professional levels[27].

Experience from the Danish General Population study on FH[14] suggests that development of national models of care, and health policy integrating care between GPs and specialists, would achieve the best outcomes for individuals and families with FH.

Density of population in close geographic proximity can help the cascade screening of relatives, with families in more remote locations and migrant families at a much greater risk of having a less effective service[22, 68].

Where does primary care screening for FH fit into Models of Care?

The role of primary care in the detection and care of patients with FH is evolving but no consensus exists on the optimum screening strategy, on how best to integrate primary and specialist level care[32], on genetic versus phenotypic testing[3, 34, 69], on

childhood screening[70], on sustainable methods of cascade testing close relatives of index cases[71] and on recording family history[72, 73]. **Table 2** provides suggested strategies for measuring cholesterol and genetic testing by age in a primary care practice. Low levels of public and health professional awareness of the disorder is central to this uncertainty as is poor compliance once a diagnosis is made[9, 50].

The traditional model of care for FH is based on the chronic care model[3, 32] and aims to deliver the right treatment, for the right patient, at the right time, by the right team across the continuum of care. Of necessity, this will involve a major contribution from primary care but patients with the condition are not being recognised during routine clinical encounters[1, 9, 14]. The current infrastructure in primary care makes cascade screening very challenging[3, 22]. Research in UK estimated an upper limit of 40% success rate might be possible and that involved specialist centre supports[34]. Attempts at cascade testing in primary care have been limited but the option is being canvassed[47]. Tertiary hospital models of service delivery are unlikely to be sustainable in primary care. Targeting high risk individuals with family history of premature CVD would be useful[9, 32, 33, 36].

Unanswered questions on primary care detection of FH

From this review, we propose new lines for research based on a framework proposed by Gidding et al in an American Heart Association statement on FH[1]. **Table 3** summarises topics that cover new diagnostic applications, population science, clinical research, patient-centric questions and models of care. Public consultation regarding all research aspects, particularly detection methods such as universal screening is recommended[74].

The challenge of identifying new index cases of FH in the community setting[75] requires much more than opportunistic case finding during routine GP consultations, followed by cascade testing of close family relatives[76]. Universal screening approaches together with reverse cascade testing in the child-parent setting has shown good potential,[40, 41, 77] but should be seen as part of a multi-faceted approach across community and hospital clinic settings that is integrated into routine clinical care[75].

The potential of FH Registries[78-81] and improved coding for FH needs to be linked to screening approaches and establishment and harmonisation of the clinical diagnosis[1, 26, 77]. Primary care has a key role to play but lacks the infrastructure and supports offered by hospital lipid clinics. Such support will be critical if a sustainable primary care based model of care is to be established[1].

Conclusion

Primary care can improve the detection and care of FH patients through an efficient, cost-effective and sustainable approach acceptable to patients, families and health professionals[1, 3, 9]. This approach should straddle the entire continuum of care[3, 9, 32, 82] – general practice, lipid specialists, cardiology, paediatrics, endocrinology, pathology, genetics and allied health. FH is best diagnosed in childhood or early adolescence[1, 9, 12, 14] followed by cascade testing of family members with 50% detection rates expected among first degree relatives[1, 26, 64, 65]. This allows for timely institution of lifelong medication and lifestyle changes to prevent the early development of atherosclerosis[3, 9, 12,]. A shared care model involving primary care for low risk and specialist support for high risk and difficult to manage patients, would be ideal.

Increased awareness of potential FH among the public and among health professionals is required[1, 50]. GPs and PNs should grasp the implications of a diagnosis of FH[1, 3, 9, 12, 50], and the need for follow-up checks to monitor compliance and treatment targets[1, 9, 12, 14, 50]. Patients need re-enforcement that achieving LDL-c targets will reduce their cumulative lifetime risk for premature CAD[12, 50]. Chronic disease care plans are a cost-effective way for general practice to manage such care[22, 58].

At community level, families with history of early heart disease should be especially targeted[1, 3, 12]. Primary care with its ease of access and frequent patient contact can help in this regard[18, 19] Patients and families with FH need reminding that they are at significantly greater risk for CVD compared to those without[50]. Better education for the newly diagnosed young and regular follow-up to ensure compliance will be necessary[12, 82]. Wald et al's[40] targeting of 92 general practices to universally screen over 10,000 toddlers aged 1-2 years at routine immunisation attendances with 84% parent approval offers hope for the future. Childhood detection allowed reverse cascade screening of parents (50% pickup) and saved lives[40].

A combination of opportunistic case-finding, systematic and universal screening of general practice databases[33, 36, 47] increased public and health professional awareness of the disease[1, 3, 9, 14], and better education and treatment knowledge among primary care teams[1, 50], especially the need for lifetime care with specialist support, is required.

Conflicts of Interest:

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Table 1. Screening criteria for FH and role and opportunities for primary care

Screening Criteria	
(1) The screening programme should respond to a recognised need	• Over 85% of patients with FH have not been identified[2]. • Without treatment CHD develops[1, 3, 9].
(2) The objective of screening should be defined at the outset.	• Identification of patients at very high risk of premature CHD[1, 3, 9]. • High intensity lipid lowering treatment can lead to 48% reduction in CHD mortality[1, 3, 9].
(3) There should be a defined target population.	Less consensus, but is based on an interplay of an individual's cholesterol levels and family history of premature coronary heart disease, familial hypercholesterolemia and/or raised cholesterol eg: • Cholesterol levels > 9.3 mmol/l indicated FH in 28% of patients[60] • Cholesterol levels > 7.5mmol/l should trigger further assessment of FH[2, 35] • Personal or family history of premature CHD[17] • Diagnostic criteria such as the DLCN[42], MEDPED[43] and S-B criteria[44]
(4) There should be scientific evidence of screening programme effectiveness.	Case series and interventional studies[49] show improvement in the number of new cases identified with possible or definite FH.
(5) The programme should integrate education, testing, clinical services and programme management.	Several countries integrate preventative programmes and care pathways from primary to specialist care [1, 3, 9] (see section "Potential approaches to screening in primary care").
(6) There should be quality assurance, with mechanisms to minimise potential risks of screening.	• Lipid tests are available to internationally recognised standard (currently ISO 17043 in UK and NPAAC[83] in Australia) • Family history recording of a three generation pedigree is standard in specialist care but the requirement for primary care is unclear. This could be a detailed family history collection or a less sensitive method of a few direct questions[84] • Genetic testing will require agreed standard of testing and interpretation prior to adoption. Currently the gold standard is NGS[69, 85, 86] as a cost saving method[87,88] but risks missing phenotypic FH[3].
(7) The programme should ensure informed choice,	• Patients offered genetic testing within standard ethical framework including fully informed of the implications of testing [3, 89].

confidentiality and respect for autonomy.	• Cholesterol testing is offered as part of routine clinical care - implications for testing and detection of FH may not be appreciated initially [45].
(8) The programme should promote equality and access to screening to the entire target population.	Identification of FH in primary care could involve opportunistic identification at review by GP or through programmes such as the UK national vascular check programme[59] which has improved assessment in deprived communities[90].
(9) Programme evaluation should be planned from the outset	From inception of an FH screening programme in primary care, key measures assessed should include: • process measures such as recruitment rate and specialist care attendance rate • outcome measures such as identification rates of FH and proportion of confirmed FH patients treated to target
(10) The overall benefits of screening should outweigh the harm.	• Reducing premature CHD is the prime target of FH screening[1, 3, 9]. • The false positive diagnostic rate[44] is a potential harm but better use of algorithms (FAMCAT[36] and TARB-Ex[33]) may increase specificity • The psychological impact of a diagnosis is considered minimal but evidence for short-term increase in anxiety is recognised [56, 57]

FH: Familial hypercholesterolaemia

CHD: Coronary Heart Disease

DLCN: Dutch Lipid Clinic Network

MEDPED: Make Early Diagnosis to Prevent Early Deaths

S-B: Simon-Broome

NPAAC: National Pathology Accreditation Advisory Council

DNA: Deoxyribonucleic Acid

NGS: Next Generation Sequencing

FAMCAT: Familial Hypercholesterolaemia Case Ascertainment Tool

Table 2. Tentative recommendations for screening by age for FH in primary care

Age (years)	Cholesterol Testing	Genetic Testing	CASCADE testing if patient is index case	CASCADE testing if first degree relative positive
0-2	No, unless both parents have high cholesterol	Both parents gene positive	Test parents and siblings	Both parents positive (elevated cholesterol or gene positive)
2-11	> 2 years with positive family history; otherwise between age 5 and 11 by guidelines	LDL-c > 190 mg/dL and positive family history	Test parents and siblings	Parent or sibling gene positive
12-30	If not tested previously, optimally by age 21 years	Meet S-B, DLCN, MEDPED or other criteria for phenotypic FH	Test parents and siblings	Parent or sibling gene positive
30-60	Per adult guidelines	Meet S-B, DLCN, MEDPED or other criteria for phenotypic FH	Test all first degree relatives	Parent, sibling, or child gene positive
> 60	Per adult guidelines	Meet S-B, DLCN, MEDPED or other criteria for phenotypic FH	Test all first degree relatives	Child or sibling gene positive

FH: Familial hypercholesterolaemia

LDL-c: Low Density Lipoprotein-cholesterol

S-B: Simon-Broome

MEDPED: Make Early Diagnosis to Prevent Early Deaths

DLCN: Dutch Lipid Clinic Network

Table 3. Knowledge gaps and suggestions for future research on FH screening in primary care.

Science: Analytical Methods • Assessment of role cholesterol gene scores in testing for FH • Development of point-of-care lipid testing - total and LDL-cholesterol and Lp(a) • Development of point-of-care DNA testing • Compare genomic strategies Sequence vs Chip & Sequence
Epidemiology • Identification of new gene founder populations • Genetic epidemiology of FH in diverse communities • Development and application of registries • Development and testing of universal screening protocols • Data linkage studies between primary care and specialist databases
Clinical Research (diagnostics, risk prediction, intervention trials) • Risk communication of genetic variants • Role of risk prediction algorithms in screening for FH • Clinical trials of screening protocols and testing interventions • Enhancing cascade testing methods in the community • Perceptions and psychological sequelae of genetic testing • Development of new selective screening protocols • Enhancing the use of information technology in case detection
Patient-centric • Health literacy and understanding of genomics and genetic testing • Education of public and patients on genomics and role in healthcare • Insurance implications of genetic testing • Public consultations regarding screening methods for FH • Advocacy for raising awareness about genomics and genetic testing
Models of Care • Education of primary care health professionals in genomic medicine • Development and testing of primary care based models • Roles of Specialists, General Practitioners, Practice nurses and Pharmacists in detection and follow-up • Design of education, training and accreditation programs in genomic medicine • Incorporation of cascade testing for Lp(a) within a primary care model

FH: Familial hypercholesterolaemia

LDL: Low Density Lipoprotein

Lp(a): Lipoprotein(a)

DNA: Deoxyribonucleic Acid