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ARTICLE

Improving Familial Hypercholesterolemia Detection Through Implementation of Nurse-led Cascade Screening

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Abstract

Aims/Background Familial hypercholesterolemia (FH) is a genetic disorder that leads to premature cardiovascular disease. Early detection and treatment are crucial for reducing morbidity and mortality. This study describes the development and impact of a nurse-led cascade screening service in Northern Ireland (NI).

Methods A retrospective cross-sectional analysis and audit of data from 2010 to present was conducted using patient databases, clinical notes, and electronic records.

Results An estimated 6925 individuals in NI have FH, with 26.9% identified (1866/6925). The mean detection rate per proband was 3.2 cases. The average age of diagnosis was 46.7 years for probands and 36.1 years for the FH population as a whole (35.1 for males, 36.9 for females). Excluding children (<18 years), the adjusted mean age was 43.7 for males and 44.4 for females. The overall male-to-female ratio was 0.817 (824 males:1008 females). Six common mutations in the low-density lipoprotein receptor (*LDLR*) and apolipoprotein B (*APOB*) genes account for 40% of cases, and 16.7% were diagnosed before age 16. NI benefits from a favourable FH nurse-to-population ratio (1:380,000).

Conclusion Nurse-led cascade screening has enabled NI to surpass the National Health Service (NHS) 'Long Term Plan' target of 25%, demonstrating sustained high detection rates, particularly among females and children. Ongoing funding is essential to further expand the service and support the continued development of the FH nurse role.

Key words: familial hypercholesterolemia; cascade; screening; low-density lipoprotein; cardiovascular disease

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Introduction

Familial hypercholesterolemia (FH) is a genetic disorder characterised by elevated low-density lipoprotein cholesterol (LDL-C) levels, resulting from abnormalities in the low-density lipoprotein receptor (LDLR) or related cellular apparatus (McGowan et al, 2019). In the majority of cases, mutations in the *LDLR* gene inherited in a heterozygous, autosomal dominant pattern lead to functional impairment of the LDLR (i.e., heterozygous FH (HeFH)). Less commonly, mutations in the apolipoprotein B (*APOB*) and proprotein convertase subtilisin/kexin type 9 (*PCSK9*) genes can also cause FH or inheritance in the homozygous pattern (HoFH)

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(Diboun et al, 2022). Screening efforts primarily focus on identifying individuals with HeFH due to its greater prevalence and the potential for effective intervention. Individuals with FH are at a significantly increased risk of atherosclerotic cardiovascular disease (ASCVD) (Zhang et al, 2024).

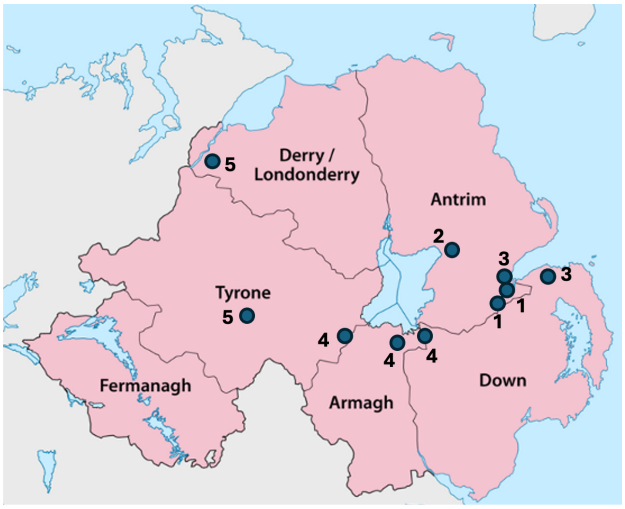
FH is underdiagnosed but has an estimated prevalence of 1 in 250–300 (Akioyamen et al, 2017), with around 250,000 affected individuals in the United Kingdom (UK) and around 15,000 (6%) having a formal genetic diagnosis (Ingoe et al, 2021). Early detection and prompt initiation of treatment are key strategic public health priorities for the National Health Service (NHS) (NHS England, 2019). Several patient advocacy groups, including the Northern Ireland Chest, Heart & Stroke (NICHS), Heart UK, and FH Europe, are actively involved in promoting awareness and support for those affected. Despite increased awareness and published guidance from the National Institute for Health and Care Excellence (NICE) (NICE, 2019), numerous challenges contribute to persistently low detection rates.

The advent of cascade screening in high-income countries has led to an increase in the identification of non-index cases (Knowles et al, 2017). This progress has garnered international recognition, with collaborations such as the European Atherosclerosis Society (EAS) Familial Hypercholesterolemia Studies Collaboration (FHSC) and the World Health Organization (WHO) (Vallejo-Vaz et al, 2018, 2021) calling for widespread improvements in early detection and treatment to reduce morbidity and mortality associated with this condition. In the Netherlands (Dickson et al, 2023) genetic results from probands were shared with national foundations, who then contacted the patient to facilitate cascade screening, leading to the identification of 70% of cases nationwide. These strategies improved FH cascade testing uptake compared to previous estimates. Similarly, innovative cascade strategies in the United States of America (USA) (Jones et al, 2024) have shown increased detection of non-index cases. Despite these advances, challenges persist, especially in addressing the logistical barriers to widespread implementation. A nurse-led cascade screening model offers a promising solution to these issues.

Northern Ireland (NI) is a devolved nation within the UK, located in the northern part of the island of Ireland, off the northwestern coast of mainland Europe. It covers a land area of 14,130 km^2 and, according to the 2021 census, has a population of approximately 1.87 million (NISRA, 2021). Based on an expected prevalence of 1 in 250 to 300, the estimated number of individuals with FH in NI ranges from about 3800 to 7600. There are five major healthcare provider organisations, known as Health and Social Care (HSC) trusts, each consisting of various hospitals that offer lipid clinics primarily led by chemical pathologists (see Fig. 1). Additionally, each trust is supported by one specialist FH nurse.

Diagnosis and Treatment of FH

Several diagnostic criteria are used to identify FH, with the Simon Broome (Scientific Steering Committee on Behalf of the Simon Broome Register Group, 1991) and Dutch Lipid Clinic Network (DLCN) criteria (Nordestgaard et al, 2013) being the most common. These systems assess the likelihood of FH based on LDL-C levels, family history, and clinical signs. In NI, a modified DLCN version is used.



1. **Belfast Health and Social Care Trust**
   - Royal Victoria Hospital, Belfast
   - Belfast City Hospital, Belfast
2. **Northern Health and Social Care Trust**
   - Antrim Hospital, Antrim
3. **South-Eastern Health and Social Care Trust**
   - Ulster Hospital, Dundonald
   - Ards Hospital, Newtownards
4. **Southern Health and Social Care Trust**
   - Craigavon Hospital, Craigavon
   - South Tyrone Hospital, Dungannon
   - Banbridge Polyclinic, Banbridge
5. **Western Health and Social Care Trust**
   - Altnagelvin Hospital, Derry
   - Omagh Hospital and Primary Care Complex, Omagh

Fig. 1. Five main HSC trusts, with an individual FH nurse numbered and dots mark hospitals which provide chemical pathology consultant led lipid clinics in NI. HSC, Health and Social Care; FH, Familial hypercholesterolemia; NI, Northern Ireland.

Studies show poor phenotype-genotype correlation in FH, indicating that even mild cases should be screened, with the DLCN offering the most detailed assessment (Catapano et al, 2016; Vrablik et al, 2020). Once a proband is identified, cascade screening and genetic testing, including for children under 11, are initiated.

FH treatment in NI follows NICE guidelines (NICE, 2019), with high-intensity statin therapy and lifestyle changes as the standard. The recent EAS/European Society of Cardiology (ESC) dyslipidaemia guidelines (Catapano et al, 2016) recommend lower LDL-C targets to reduce ASCVD risk, though they have not been fully endorsed in NI due to cost-effectiveness considerations in a publicly funded healthcare system.

Development of NI FH Diagnostic Service

The FH diagnostic service was established in 2000 as a regional genetics service, following earlier ad hoc testing. It enables early detection through multigenerational testing of probands and cascade cases. The Regional Molecular Diagnostics Service at Belfast City Hospital handles diagnostics, while chemical pathologists in the five HSC trusts manage FH patients, supported by paediatric services

at Belfast Health and Social Care Trust (BHSCT) and Northern Health and Social Care Trust (NHSCT). In 2014, the Department of Health formally recognised the service and funded specialist FH nurses in each trust, enabling the creation of a nurse-led cascade screening program. These nurses play a key role in guiding families through testing, providing counselling, and expanding service capacity. Referrals for genetic testing come from various healthcare settings. The pathway for cascade screening is shown in Fig. 2.

Although there has been an increased emphasis on early detection, small-scale pilot projects in cardiac rehabilitation and general practice database searches have not yielded significant results, according to anecdotal observations. However, patient and public involvement initiatives have improved community awareness of FH.

The aim of this study is to describe the developments and achievements of the FH diagnostic service in NI, with a focus on the nurse-led cascade screening model and its impact on increasing detection rates for proband and non-index cases. The service will be detailed to provide a model for replication in other settings.

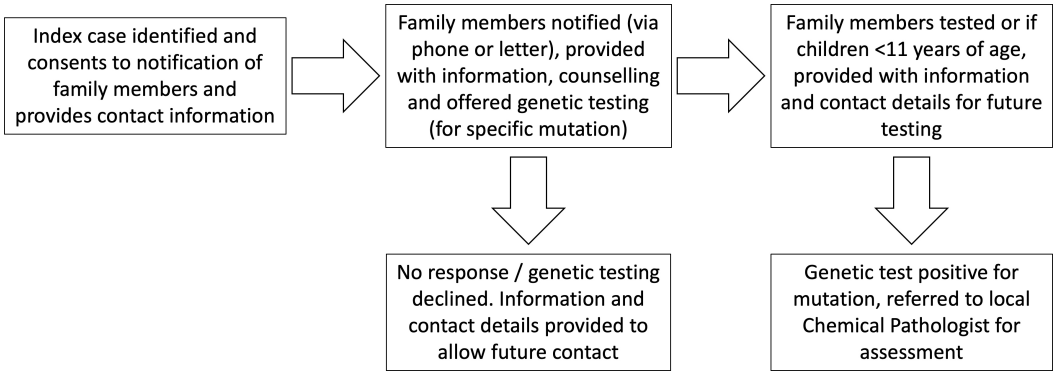


Fig. 2. Pathway for nurse-led cascade screening when proband has been detected.

Methods

A retrospective cross-sectional analysis and audit was conducted on data collected from 2010 to the present (approximately 15 years), using patient databases, clinical notes, and electronic care records. Only patients with a confirmed genetic diagnosis and complete, accurate data were included, while those with partial or missing data were excluded. All relevant information regarding probands and confirmed FH cases is maintained in a centralised database (STARLIMS® laboratory integrated management software, ©2024 STARLIMS Corporation, Hollywood, FL, USA). This database is managed by the FH nurses and accessible to the multidisciplinary team (MDT) across NI ensuring coordinated care and management. For patients diagnosed prior to the availability of electronic records, all relevant data, including genetic information, was reviewed to verify the accuracy of the diagnosis.

The study adhered to local trust guidelines, ensuring patient confidentiality and data protection throughout the process. In accordance with the Declaration of

Helsinki, individual consent was not required, as the study utilised anonymised data and did not involve direct intervention with participants. This work was conducted as part of a service improvement initiative aimed at enhancing the efficiency and effectiveness of the FH screening program therefore formal ethical approval was not required.

Data analysis was performed using Microsoft Excel® (Microsoft Excel®, version 2021, Microsoft Corporation, Redmond, WA, USA) to identify trends and generate graphical representations of the results. Figures were created using Adobe Illustrator® (Adobe Illustrator® 2021, Adobe Inc., San Jose, CA, USA). Means were calculated to provide a snapshot of key outcomes (namely sex and age) and allow subgroup analysis. Frequencies of detection rates and characteristics (e.g., age and sex) were presented as proportions and percentages. The inclusion criteria were limited to patients with complete records within the specified timeframe, while those with incomplete data were excluded.

Results

Since 2010, approximately 8000 patients in NI have been tested for FH. However, the actual number is likely to be significantly higher, as data management software (STARLIMS®) was only implemented in that year. To date, 419 probands and their families have been identified, resulting in a total of 1866 FH patients currently under review in secondary care. While the prevalence is reported in the literature as 1:250–300, we use a prevalence estimate of 1:270, which suggests there are approximately 6925 individuals with HeFH in NI. As of now, we have identified 26.9% (1866/6925) of this estimated population, based on the latest census data and population size (see Fig. 3).

The implementation of the nurse-led cascade screening service in 2014 has led to a mean of 6.9 family members being tested for each proband. This has resulted in the identification of new FH cases at a mean detection rate of 3.2 per proband. Between 2010 and 2014, there was a mean detection rate of 68 cases per year (excluding cases at 2010 baseline and taking the mean of cases detected in 2011–2014). There was a peak mean detection rate of 101 cases per year from 2014 to 2020 (excluding cases at 2014 and taking the mean of cases between 2015–2020). Although detection rates declined during the coronavirus (COVID-19) pandemic, they have begun to rise again as services resume (see Fig. 4).

Demographics

Demographic information was available for 98% (1832/1866) of individuals in the FH population, which includes both probands and patients identified through cascade screening. The mean age at diagnosis is 36.1 years, with males diagnosed at a mean age of 35.1 years and females at 36.9 years. When excluding children under 18 years, the adjusted mean age rises to 43.7 years for males and 44.4 years for females. The overall male-to-female ratio in this population is 0.817 (824:1008), indicating a higher proportion of females in both the proband subgroup and the total population.

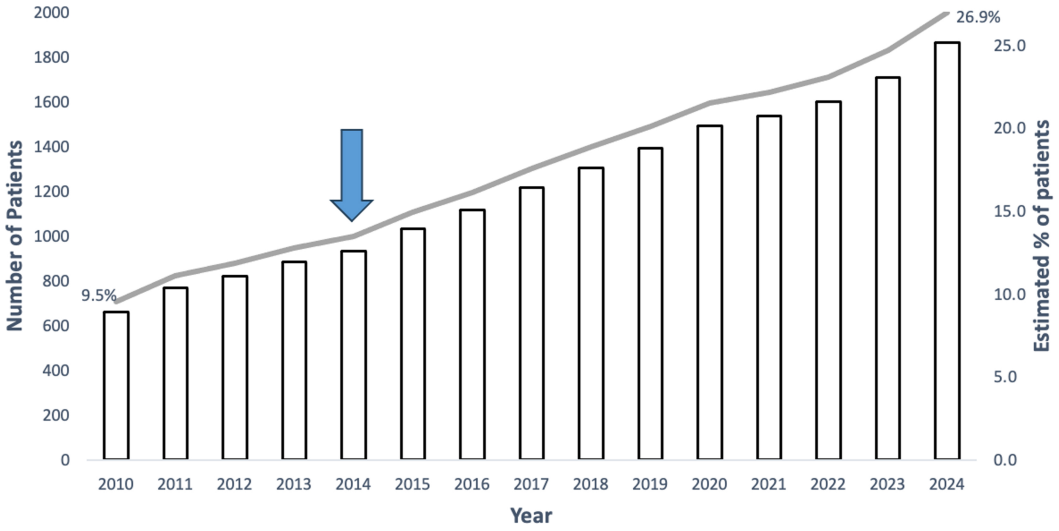


Fig. 3. Cumulative detection rates of FH in NI. Bar chart demonstrating numbers of FH patients detected (Y axis) per year (X axis). Cumulative % detection rate of estimated cases is also shown based on prevalence of 1:270 and population size from census data (NISRA, 2021). Blue arrow indicates introduction of FH nurses.

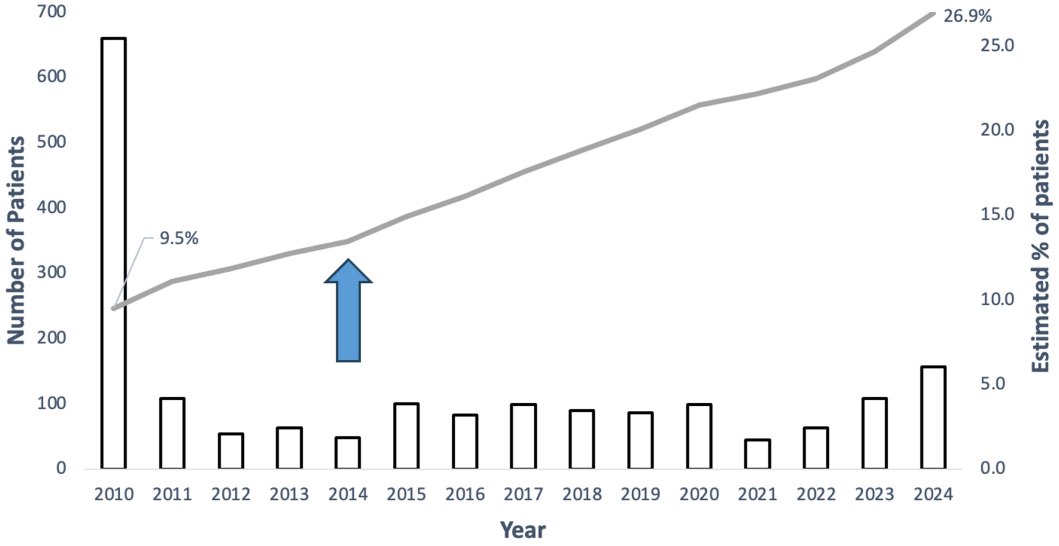


Fig. 4. Absolute numbers of FH patients detected per year. Bar chart demonstrating absolute numbers of FH patients detected (Y axis) per year (X axis). Cumulative % detection rate of estimated cases is also shown based on prevalence of 1:270 and population size from census data (NISRA, 2021). Blue arrow indicates introduction of FH nurses.

In probands specifically, the mean age at diagnosis is 46.7 years (excluding children under 18 years). Notably, there is a significant paediatric population, with 23.8% (444/1866) diagnosed before the mean age of 18, and 16.7% (311/1866) diagnosed before the age of 16. As patients transition from paediatric to adult services after age 16, this group currently represents 9.4% of the total population (176/1866) (see Table 1).

Table 1. Demographic information of FH population in NI.

All patients				
Ratio M:F	824:1008 (0.817)			
	Males		Females	
Mean age at diagnosis (years)	35.1	824/1832 (45.0%)	36.9	1008/1832 (55.0%)
Adults				
≥18 years	43.7	609/824 (73.9%)	44.4	779/1008 (77.3%)
Children				
<18 years	10.6	215/824 (26.1%)	11.2	229/1008 (22.7%)
<16 years	9.7	118/215 (54.9%)	10.2	193/229 (84.3%)
Index case (Probands)				
Ratio M:F	155:264 (0.587)			
	Males & Females			
Mean age at diagnosis (years)	46.0		419/1832 (22.9%)	
Adults				
≥18 years	46.7		409/419 (97.6%)	
Children				
<18 years	14.0		10/419 (2.4%)	
<16 years	11.1		5/10 (50%)	

Subgroup analysis is based on population as whole (proband and non-index or cascade patients) and probands. Means are displayed with absolute numbers and percentages. M:F, males:females.

Molecular Analysis

If the index patient is suspected of having FH, genetic testing is carried out. Historically, undifferentiated testing utilised temporal temperature gradient electrophoresis (TTGE) for specific *LDLR* exons and Sanger sequencing for the *APOB* c.10580G>A mutation. This approach evolved in 2006 to include an iPLEX MassARRAY panel (Agena Bioscience®, Agena Bioscience 4755 Eastgate Mall, San Diego, CA, USA) covering 57 common FH mutations, along with high-throughput Sanger sequencing of the *LDLR* promoter and exons, *PCSK9*, and *APOB* regions. In 2014, the FH-I/FH-II Biochip array (Randox®, ©2024 Randox Laboratories Ltd., Crumlin, UK) replaced previous methods, screening for 40 common mutations and utilizing Sanger sequencing and multiplex ligation-dependent probe amplification (MLPA). By 2020, next-generation sequencing (NGS) was adopted, employing an exome panel that included *APOB*, apolipoprotein E (*APOE*), *LDLR*, low-density lipoprotein receptor adaptor protein 1 (*LDLRAP1*), and *PCSK9* to streamline the testing process. Nurse-led cascade screening focuses on targeted testing based on known mutations identified in index cases (probands). Once a proband's mutation is confirmed, family members can undergo targeted genetic testing for the known mutation. NI has five FH nurses (one per trust) giving a nurse-to-population ratio of 1:380,000.

Table 2. Mutation types of FH in NI.

Number of families	Percentage total	Mutation type
56	13.0%	*APOB* c.10580G>A p.(Arg3527Gln)
17	6.7%	*LDLR* c.1845+11C>G
9	6.5%	*LDLR* c.933del p.(Glu312Serfs*58)
21	4.8%	*LDLR* c.2292del p.(Ile764Metfs*2)
20	4.5%	*LDLR* c.1444G>A p.(Asp482Asn)
7	4.0%	*LDLR* c.1432G>A p.(Gly478Arg)

The top six mutations in low-density lipoprotein receptor (*LDLR*) and apolipoprotein B (*APOB*) are displayed along with the number of families and percentage of total.

Approximately 140 different mutation types have been identified, with six common mutations in *LDLR* and *APOB* accounting for 40% of those observed in our FH population. Table 2 displays these six most common mutations, with *LDLR* mutations comprising the largest proportion. Notably, there is a predominance of a single *APOB* mutation, c.10580G>A (p. (Arg3527Gln)), which leads to the phenocopy disorder familial defective apolipoprotein B-100 (FDB).

Discussion

NI continues to have a high detection rate of FH both in probands and non-index (cascade) cases. Currently, we have identified approximately 26.9% of the estimated FH population, surpassing the 25% target set by the NHS 'Long Term Plan' in 2019 (NHS England, 2019). This achievement is largely attributed to the capacity for increased testing facilitated by the nurse-led cascade screening service. Improved information and the use of healthcare professionals other than physicians has been identified as a key factor in increasing screening uptake, with better communication leading to higher participation rates (Jones et al, 2024). In Wales and Wessex, however, less than a third of relatives of a proband are tested for FH and opportunities for improvement have been identified as integrating geographically dispersed families into cascade testing, directly contacting relatives when possible, and exploring new strategies to boost participation, particularly among men (Cox et al, 2024). Similarly, NI faces geographical challenges but has overcome this along with increased capacity through a team of dedicated FH nurses that contact potential screening candidates directly. NI benefits from a favourable ratio of one FH nurse for every 380,000 population, enhancing the efficiency of the cascade screening program. The inclusion of FH nurses in the MDT has increased capacity to see new referrals and identify probands in the lipid clinic, as the screening function previously was managed solely by consultants pre-2014. While our overall detection rates surpass those of other UK regions, it is important to recognise our smaller population size. Our detection rates may also be higher due to established pathways within primary care, efforts to raise awareness, and strong collaboration among Chemical Pathologists, Clinical Scientists, and FH nurses.

In the UK, approximately 93% of FH patients have mutations in the *LDLR* gene, 5% in *APOB*, and 2% in *PCSK9* (Myant, 1993; Sharifi et al, 2017). Similarly, *LDLR* mutations make up the majority of detected mutations in NI, where we observe a higher prevalence of the *APOB* mutation c.10580G>A p. (Arg3527Gln) compared to other regions. While this specific mutation is routinely screened in modern testing panels, it underscores the importance of comprehensive testing across various genes and mutation types to identify pathogenic variants. Before the introduction of NGS, we relied on various commercial panels, highlighting the economic feasibility of providing diagnostic or screening services in lower-income settings. Similarly, cascade screening proves to be highly cost-effective compared to diagnostic proband testing, as the mutation has already been identified (Marquina et al, 2024).

The mean age of diagnosis in our cohort aligns with that of the broader UK population, as reported by the FHSC registry (Vallejo-Vaz et al, 2021). Interestingly, we observed a higher female-to-male ratio in our data compared to other cohorts (Vallejo-Vaz et al, 2021; Zamora et al, 2023). While we cannot definitively explain this finding, it could reflect gender differences in healthcare-seeking behaviour in NI. Females with FH are typically reported to be diagnosed later and are more likely to be untreated (Iatan et al, 2024). It is also possible that milder FH phenotypes, which are more prevalent in females, may be overlooked by diagnostic tools such as the modified DLCN. Although population-based, undifferentiated genetic screening could improve detection rates, it must be carefully balanced with considerations of cost-effectiveness and laboratory capacity (Goldberg et al, 2011).

NI currently has a substantial paediatric FH population, comprising 9.4% (176/1866) of the total, reflecting the success of the screening program and commitment to early detection. Furthermore, 23.8% (444/1866) of the total population was diagnosed before the age of 18, with 16.7% (311/1866) diagnosed before age 16. This highlights the need for adequately funded services with appropriate paediatric support, as early identification allows for timely statin therapy in accordance with NICE guidance (NICE, 2019). Two of the major healthcare providers (BHSCT and NHSCT) include paediatricians in the care of patients under 16, while in other clinics, paediatric patients are evaluated by Chemical Pathologists alongside their parents. A more effective model might involve having a paediatrician with an interest in lipid disorders.

A potential challenge in expanding cascade screening more broadly is the recruitment of qualified FH nurses and ensuring they receive appropriate training to effectively manage the increasing demand for screening and ongoing patient care. There is significant potential to expand the role of FH nurses beyond cascade screening, a shift that is actively being adopted in NI. Their unique skills position them ideally for expanding current services to include the delivery of novel injectable therapies and treatments. It is essential that this important work is recognised, strategically planned, and adequately funded. With a growing FH population, the ongoing focus should incorporate delivering effective preventative treatment to improve patient outcomes.

Strengths and Limitations

Retrospective observational studies have inherent limitations, including the lack of a comparison or control group, which makes it challenging to draw causal inferences or determine the effectiveness of interventions. Observed outcomes may be influenced by confounding variables, and reliance on existing data can introduce biases, such as selection bias or incomplete records, potentially affecting the validity and generalisability of the findings. However, the aim of this study was to highlight the increase in detection rates and to describe the service in sufficient detail to facilitate replication by others. The strength of this study is in highlighting the scalability of a nurse-led cascade screening model and evolving role of the FH nurse.

Further research is needed to improve and expand the cascade screening model, with a focus on validating its effectiveness across different populations and countries to ensure broader applicability and optimal outcomes.

Conclusion

NI has successfully established a service for diagnosing FH, incorporating a nurse-led cascade screening model that has resulted in year-on-year increases in detection rates for both probands and non-index cases, surpassing the 25% target set by the NHS 'Long Term Plan'. The service shows high rates of detection in women and children and continued funding is essential to sustain and expand this progress, including development of the FH nurse role.

Key Points

- Familial hypercholesterolemia (FH) is a common genetic condition resulting in premature cardiovascular disease.
- Northern Ireland (NI) has surpassed the NHS 2019 'Long Term Plan' target, identifying 26.9% of FH patients.
- A nurse-led cascade screening model is scalable, enhancing the capacity for testing and detection of FH cases.

Availability of Data and Materials

All data generated or analyzed during this study are available from the corresponding author (Dr Eamon Patrick McCarron) upon reasonable request.

Author Contributions

All authors have contributed to the preparation and submission of this manuscript. EPM was responsible for conception, analysis and drafting of manuscript. CR and PHar collected and analysed data from the FH screening program. KR and PHam were responsible for clinical data and review of manuscript. MOK contributed to the conception of this article. All authors contributed to important editorial changes

in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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