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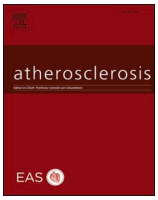

Editorial

Uncovering familial hypercholesterolaemia phenotype in the community: How primary care can transform early detection and management

Familial hypercholesterolaemia (FH) is an autosomal dominant genetic condition affecting approximately 1 in 250 individuals who inherit the common heterozygous form [1]. Despite its prevalence and the significant associated risk of premature atherosclerotic cardiovascular disease (CVD), over 80 % of individuals with FH remain undiagnosed [2]. This represents a missed opportunity, since associated increased risk of premature CVD is significantly reduced with timely and appropriate use of lipid-lowering therapy. The recent paper published by Gijon-Conde et al. in this issue of Atherosclerosis, underscores the role of primary care as an ideal place to systematically identify individuals with FH in the electronic health records (EHR) and initiate appropriate and timely management interventions [3].

1. Identification of FH in the general population

In primary care identification of possible FH clinical phenotype generally begins with identifying a very high total or low-density lipoprotein (LDL) cholesterol levels. As demonstrated by Gijon-Conde et al., using the 90th centile for cholesterol levels is a rapid and low-cost approach to search EHRs to identify individuals with suspected FH. This approach could potentially identify a significant prevalence of FH clinical phenotype, reaching 1.03 % prevalence in the study by Gijon-Conde et al. The exclusion of individuals with raised triglyceride levels, as a refinement to the initial screening, is appropriate to exclude other lipid disorders such as familial combined hyperlipidaemia.

While using the 90th centile for cholesterol levels, with appropriate refinements, offers a practical starting point for identifying FH clinical phenotypes, more elaborate approaches for searching primary care EHRs are also available. As highlighted by the authors, tools such as the Familial Hypercholesterolaemia Case Ascertainment Tool (FAMCAT) can improve detection rates for FH clinical phenotypes when applied to primary care EHRs [4]. However, the successful implementation of such search strategies, relies on the compatibility of the healthcare IT system, data quality, and comprehensive data recording of relevant predictor variables in the EHRs. It is also important to account for secondary causes of hypercholesterolaemia when screening for FH. The Gijon-Conde study addressed this by excluding individuals with raised thyroid-stimulating hormone (TSH) levels, indicative of hypothyroidism, a known secondary cause of hypercholesterolaemia. Other secondary causes, such as liver disorders or nephrotic syndrome, may also be identifiable through laboratory results or coded diagnosis in the EHR. One key challenge is accurately linking the timing of these abnormal laboratory test results with elevated cholesterol profiles. For instance, an individual with well-controlled hypothyroidism (normal TSH) may still have underlying FH, even if the TSH was raised in the past. In addition, crucial predictors of FH including a family history of premature coronary heart disease or a family history of high cholesterol, but these are often inconsistently recorded in EHRs. Ultimately, the quality, accuracy, and completeness of data recording in EHRs are critical to the success of any strategy aimed at identifying FH in the general population using EHRs.

More elaborate search algorithms, such as FAMCAT in the UK and FIND FH® in USA, have been developed using comprehensive EHR data to improve the identification of FH [4–6]. These tools aim to improve key performance metrics including detection rates, sensitivity, specificity, positive and negative predictive values, compared to traditional case-finding approaches used in lipid specialist care, like the Simon Broome and Dutch Lipid Clinical Network criteria [7]. Given the low prevalence of FH in the general population, it is important for population-based screening tools to achieve high sensitivity and positive predictive value to reliably identify true cases. However, this must be carefully balanced with an acceptable specificity and negative predictive value to minimise false positives. Excessive false positives can lead to unnecessary follow-up testing, increased healthcare cost, patient anxiety, and additional burden on already overstretched primary care systems.

Ideally, FH clinical phenotype should be genetically confirmed. While resource limitations may preclude genetic testing in low- and middle-income country settings, the identification of FH clinical phenotype alone at a population level will improve health outcomes. As the cost of genetic testing decreases, there would be the opportunity to expand genetic testing in the community and subsequent cascade screening. Cascade screening of relatives of identified index cases, is crucial to identify other family members at an early age before the development of significant atherosclerosis and this has been shown to be highly cost-effective for FH [8,9]. The International Atherosclerosis Society (IAS) and other guidelines support cascade screening as an effective way to find FH beyond index patients and prevent atherosclerotic CVD in families at risk of FH [10]. Fig. 1 displays a potential pathway from EHR search.

As Gijon-Conde et al. note, there is currently a lack of evidence from intervention studies evaluating different EHR-based search strategies for improving the identification of FH in the general population [11]. Despite the lack of robust evidence from randomised controlled trials, national guidelines still recommend systematic approaches. This is supported by findings from population-based EHR studies across multiple clinical sites, such as the study by Gijon et al. and others, which have successfully identified individuals with clinically or genetically

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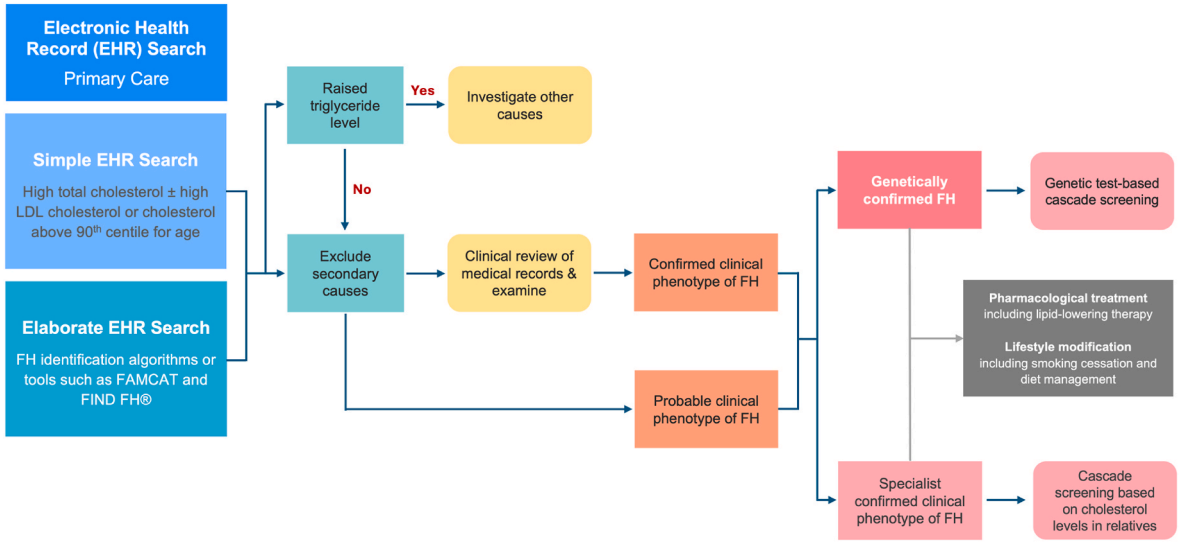

Fig. 1. Potential pathway from identification of familial hypercholesterolaemia using an electronic health record search strategy.

confirmed FH [3,7]. The recently published IAS guidance, for instance, recommends digital EHR searches and laboratory alerts to improve FH case detection [10]. These recommendations reflect a broader consensus that, while the most effective EHR-based strategies are still evolving, active case-finding in primary care should be pursued.

2. Management of familial hypercholesterolaemia

The identification of FH clinical phenotype is only the initial step in a primary care physician's involvement with the management of individuals with FH. The primary goal of FH management is to achieve substantial reduction in LDL cholesterol levels to guideline-recommended targets. The European Atherosclerosis Society (EAS) and European Society of Cardiology (ESC) Guidelines, alongside EAS Consensus Statements, provide stringent recommendations for LDL cholesterol reduction. For very high-risk individuals, which typically includes FH patients, the 2019 ESC/EAS Guidelines recommend an LDL cholesterol target of less than 1.4 mmol/L (<55 mg/dL) or at least a 50 % reduction from baseline [12,13].

Despite these clear guidelines, individuals with FH clinical phenotype or genetically confirmed FH diagnosis are often inadequately treated. The Gijon-Conde study found that a low proportion of patients received higher potency lipid-lowering therapy to reduce cholesterol, and more concerningly, none achieved the recommended LDL cholesterol targets. This finding is consistent with other studies involving both individuals with FH and the general population, where nearly half of the study population did not achieve the guideline-recommended cholesterol levels [14,15].

In addition to pharmacological interventions, addressing other modifiable risk factors is essential for individuals with FH, who are at high risk of CVD. Comprehensive lifestyle modification such as smoking cessation, dietary improvements, and physical activities plays a vital role in reducing CVD risk. For instance, individuals with FH who smoke experience significantly worse cardiovascular outcomes, highlighting the importance of comprehensive risk reduction strategies and other healthy lifestyle choices [16].

3. Equitable familial hypercholesterolaemia service provision

Any successful strategy for implementing FH care should encompass both identification and management of FH, while crucially ensuring equitable access across the entire patient pathway [10]. Recent evidence highlights disparities in the management of CVD risk between men and women, both in individuals with FH and in the general population – with poorer management in women compared to men [17,18]. In the UK Simon Broome register, Iyen et al. (2020) found men were more often prescribed high-potency statins than women, even after accounting for risk [18]. This disparity was reconfirmed in the Gijon-Conde study, which found a lower proportion of women were treated with higher potency lipid-lowering therapy. These sex-based differences are not fully explained by contraindications or risk profiles, suggesting the influence of potential bias or gaps in clinical knowledge. Such inequity underscores a pressing need to identify and address systemic biases that might exist in healthcare provision that may contribute to these discrepancies, ensuring that women with FH receive care that is as intensive and appropriately effective as that provided to men, to mitigate their increased risk of CVD.

Equity concerns extend beyond sex. Socio-demographic, ethnic, and racial disparities in the diagnosis and treatment of FH have been documented [19]. Improved care and outcomes for all patients with FH, irrespective of socio-demographic factors and background, could be achieved through better education and training of primary care physicians and other health care professionals involved in FH care [20]. This training should include increased awareness among healthcare providers regarding FH diagnostic criteria, optimal management strategies, and the importance of addressing health inequities. Introducing such educational programmes to health professionals working in diverse communities would ensure more equitable and effective care is delivered across the entire population.

In conclusion, the FH clinical phenotype can be identified in primary care using either a simple search strategy, such as the 90th centile for cholesterol levels with appropriate refinements, as demonstrated in the Gijon-Conde et al. study, or more elaborate algorithms and strategies. The fundamental prerequisite for the successful implementation of any such strategies is the robustness, completeness, and accuracy of the health and care information recorded in the EHRs. However, identification is only the beginning of the patient journey. Individuals identified with the FH clinical phenotype must receive appropriate and equitable management to reduce their risk of premature CVD and death. This goal is achievable even in settings where genetic testing for FH is not readily available, provided there is a concerted effort to ensure early diagnosis and effective treatment aligned with guideline-recommended targets for cholesterol levels.

Declaration of competing interest

The authors declare no conflict of interest.

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Ralph K. Akyea, Nadeem Qureshi*

PRISM Research Group, Centre for Academic Primary Care, School of Medicine, University of Nottingham, UK

* Corresponding author. PRISM Research Group, Applied Health Research Building (42), University of Nottingham, Nottingham, UK.
E-mail address: nadeem.qureshi@nottingham.ac.uk (N. Qureshi).