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ORIGINAL RESEARCH

EMERGING TECHNOLOGIES AND INNOVATIONS

A Scoping Review of Electronic Health Records–Based Screening Algorithms for Familial Hypercholesterolemia

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ABSTRACT

BACKGROUND Familial hypercholesterolemia (FH) is a common genetic disorder that is strongly associated with premature cardiovascular disease. Effective diagnosis and appropriate treatment of FH can reduce cardiovascular disease risk; however, FH is underdiagnosed. Electronic health record (EHR)-based FH screening tools have been previously described to enhance the detection of FH.

OBJECTIVES This scoping review explored the available literature on the performance and utility of existing EHR-based FH screening algorithms or tools.

METHODS We searched PubMed, CINAHL, and Embase from inception to October 2023 for relevant literature on the performance, utility, and/or implementation of EHR-based screening algorithms for FH.

RESULTS Of 14 screening algorithms and/or tools identified in the 27 studies included in this review, Familial Hypercholesterolemia Case Ascertainment Tool (1, 2, and ML), FIND FH algorithm, Mayo SEARCH, and TARB-Ex demonstrated the highest performance metrics for identifying patients with FH.

CONCLUSIONS EHR-based screening tools hold great potential for improving population-level FH detection. Lack of established diagnostic criteria that can be applied across diverse populations and the lack of information about the performance, utility, and implementation of current EHR-based screening tools across diverse populations limit the current use of these tools. (JACC Adv. 2024;3:101297) Crown Copyright © 2024 Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

ASCVD = atherosclerotic cardiovascular disease

CVD = cardiovascular disease

DLCN = Dutch Lipid Clinic Network

EHR = electronic health record

FH = familial hypercholesterolemia

LDL-C = low-density lipoprotein cholesterol

LR = logistic regression

ML = machine learning

NPV = negative predictive value

PPV = positive predictive value

SB = Simon Broome

Familial hypercholesterolemia (FH) is a common autosomal dominant disorder, characterized by a cumulative low-density lipoprotein cholesterol (LDL-C) burden from birth leading to significantly greater risk for premature cardiovascular diseases (CVD). FH results from a functional mutation in one of the 3 main genes regulating LDL-C metabolism: LDL receptor (*LDLR*; most common), apolipoprotein B (*APOB*), or the proprotein convertase subtilisin/kexin type 9 (*PCSK9*) gene.[1-3] Other pathogenic variants implicated in FH include mutations in the apolipoprotein E (*APOE*) gene, signal transducing adaptor family member 1 (*STAP1*), and LDL receptor adaptor protein 1 (*LDLRAP1*) gene.[4] Globally, FH affects 1 in 250 to 1 in 500 individuals.[5-8] Although recent efforts have increased the awareness, screening, diagnosis, and care of those living with FH, it remains underdiagnosed with a detection rate of <10% in the United States and lower in many countries (<5%).[5,9,10] Early identification of individuals with FH and timely interventions can reduce the risk of premature atherosclerotic CVD (ASCVD) and associated mortality by up to 80%.[11-13]

Although there are no universally accepted criteria for the diagnosis of FH, the 3 most common tools used globally include the Dutch Lipid Clinic Network (DLCN) criteria, the UK Simon Broome diagnostic (SB) criteria, and the U.S. Make Early Diagnosis to Prevent Early Death criteria (**Table 1**).[14-18] In 2015, the American Heart Association proposed a clinical classification for FH that allows FH diagnosis based on clinical criteria only or combined clinical and genetic information.[7] Scoring for most of these diagnostic criteria relies on cholesterol profile, detailed family history information, and physical examination findings, such as tendon xanthoma and corneal arcus in addition to genetic test results.[14,17,18] However, when applied to the general population, these criteria have significant limitations because details such as a family history of hypercholesterolemia, premature peripheral vascular disease or coronary artery disease, and the physical manifestations of severe hyperlipidemia are frequently missing from health records. When recorded, they are often miscoded.[19] Additionally, these criteria do not fully consider other potentially valuable, readily available information such as CVD risk factors like age, sex, and diabetes status.[20-22] Consequently, there is a need for effective alternative screening tools capable of incorporating available information from electronic health records (EHRs).

There has been a growing interest in leveraging machine learning (ML) and other established predictive models trained on EHRs to enhance the detection of FH. Studies have leveraged EHR data and ML algorithms to predict the risk of CVD.[23,24] For example, Petrazzini et al and McGilvray et al demonstrated improved accuracy, risk prediction, and reclassification for coronary artery disease and 1-year all-cause death or referral for heart failure surgical therapy, respectively, using EHR-based ML algorithms.[25,26] However, there is limited research in the field of FH that examines the performance of the current EHR screening tools, including ML algorithms, in identifying FH and their utility in improving diagnoses. Studies that describe the clinical validity (ability of a test to accurately detect/predict a patient's clinical status) [27] and utility (ability of a test to improve diagnoses and health outcomes, considering the risks and benefits associated with its use)[27] of these novel screening tools are limited. The evidence of how these tools function and are implemented among racial and ethnic minority groups, as well as in rural areas, is limited. To address this gap, we conducted a scoping review to explore the available literature on existing EHR-based screening tools being used to improve the detection and management of FH in children and adult patients. We were interested in answering the research questions: What is known from the literature and what are important gaps in knowledge regarding EHR-based FH screening tools, including their performance, utility, and implementation in diverse populations?

We had 3 main goals: 1) identify and assess the performance of existing EHR-based screening algorithms for FH across diverse populations, including racial and ethnic minority groups; 2) examine the available evidence on utility and implementation of these algorithms; and 3) understand the resulting experiences of patients and health care professionals, including gaps and challenges associated with the use of these algorithms in clinical practice.

METHODS

PROTOCOL. The protocol and research question for this review were formulated using the Population, Concept, and Context guidelines outlined in the JBI Manual of Evidence Synthesis[28] (**Table 2**). A scoping review format, which allows for a broader exploration of the available evidence, key characteristics, and the knowledge gaps related to a given field was used in this study.[29] The review was conducted in accordance with the Preferred Reporting Items for Systematic

TABLE 1 Features of Commonly Used FH Diagnostic Criteria

	DLCN	SB	MEDPED
Elevated LDL-C	Present	Present	Present
Patient with premature CAD	Present	Absent	Absent
Patient with premature PVD	Present	Absent	Absent
Tendinous xanthomata in the patient	Present	Present	Absent
Cornea arcus in the patient	Present	Absent	Absent
Evidence of FH genetic mutation	Present	Present	Absent
Family history of premature CAD	Present	Present	Absent
Family history of hypercholesterolemia	Present	Present	Present
Family history of tendinous xanthomata or cornea arcus	Present	Present	Absent

DLCN = Dutch Lipid Clinic Network; SB = Simon Broome; MEDPED = Make Early Diagnosis to Prevent Early Death; FH = familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; CAD = coronary artery disease; PVD = peripheral vascular disease.

Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) recommendations.[30] Institutional Review Board approval was not required, as publicly available data were used.

SEARCH STRATEGY. The search terms for this review were selected following consultations with a panel of experts, the research team, and a librarian from Emory University. Medical Subject Heading (MeSH) terms that aligned with the predefined inclusion criteria were used to construct a focused search strategy for identifying relevant studies. Terms such as familial hypercholesterolemia, algorithm, model, tool, electronic health/medical records were combined and refined based on the relevance of the retrieved results to the research topic. An initial literature search was performed on April 5, 2023, using PubMed. This search was subsequently replicated in CINAHL via EBSCO, and Embase on July 31, 2023. To ensure the review incorporated the most current literature, a final search in all 3 databases was conducted on October 30, 2023. The search strategy is included in the supplemental file (Supplemental Table 1). The search was restricted to studies published in English. Subsequently, downloaded search results from PubMed, CINAHL, and Embase were imported into Covidence systematic review software (Veritas Health Innovation)[31] for deduplication and screening. Additional duplicates identified during screening were manually removed.

ELIGIBILITY CRITERIA AND STUDY SELECTION. Studies that evaluated the performance, utility, and/or implementation of EHR-based screening algorithms for FH were considered eligible. Studies that reported patients' or health care professionals' experiences with the use of such algorithms were included. Studies investigating other screening tools or approaches, such as cascade screening or tools not trained on EHR data, were excluded. Additional exclusion criteria consisted of the following: 1) studies examining outcomes other than FH; 2) studies primarily focusing on the treatment and management of FH; and 3) systematic reviews, conference abstracts, research proposals, opinion papers, and other reviews.

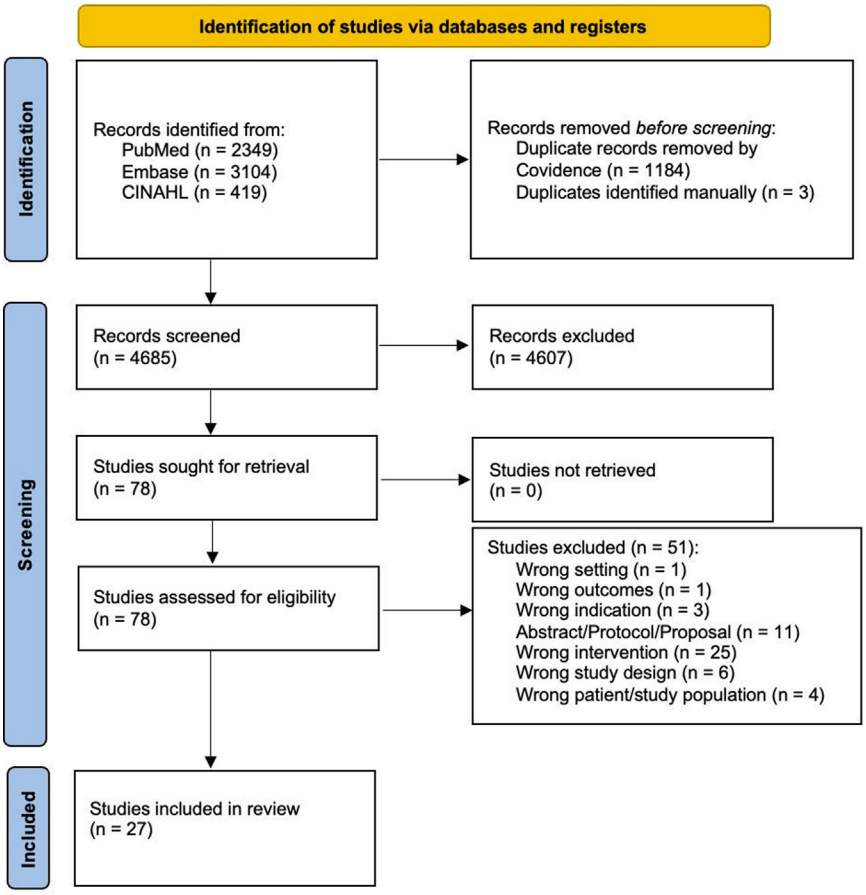
DATA EXTRACTION. Data extraction was done using Covidence software. We extracted data on study characteristics, including the first author's name, year of publication, title of publication, country, study design, and study population. We also extracted information on the characteristics of FH screening tools, including the method employed in developing the screening model, the population setting used for model development, the components of the model, and a summary of the model's performance. The studies included in this review aimed to address several objectives including 1) development, validation, and comparison of a novel algorithm for

TABLE 2 Inclusion Criteria Using the PCC Guideline by JBI Manual of Evidence Synthesis

Population
Primary care patients or patients (both pediatric and adults) from specialist clinics with EHR data, including outpatients and hospital-based patients, or EHR data from primary and/or secondary care
Individuals from the general population or community cohorts with EHR data
Concept
Studies on the performance and utility of EHR-based screening tools including machine learning algorithms and established predictive models for FH. Diagnostic accuracy test studies on models trained on clinical data available in EHRs. Studies that attempt to highlight the successes, challenges, and gaps associated with the implementation of such algorithms. Studies conducted to examine the cost-effectiveness, utility, and patients' and health care professionals' experience with the use of such screening tools.
Context
The performance and implementation across all populations including subpopulations, racial, and minority ethnic groups as well as rural areas.

EHR = electronic health record; FH = familial hypercholesterolemia; JBI = Joanna Briggs Institute; PCC = Population, concept, and context.

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analysis Diagram for Selection of Studies



identifying FH cases; 2) acceptability and feasibility of using these novel algorithms, taking into account the experiences of both health professionals and patients; 3) potential economic implications associated with the use of the novel algorithms. Performance metrics, such as sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the receiver operating curve, were recorded as reported in the reviewed studies. All studies referenced in the results are cited in the supplemental materials (Supplemental Table 2).

RESULTS

STUDY CHARACTERISTICS. A comprehensive search on PubMed, CINAHL, and Embase identified 5,872 articles. Following screening, 27 studies met the inclusion criteria. The PRISMA flow diagram (**Figure 1**) shows the selection process and results of the screening process. Among the 27 studies, 14 were conducted in Europe, 7 in North America, 4 in Asia, 1 in Africa, and 1 in Australia. Nine studies were conducted in the United Kingdom, 6 in the United States, 3 in China, 2 in Portugal, and 2 in the Netherlands. The remaining studies were from Japan, South Africa, Italy/Sweden, Canada/Australia, and Australia. Of the 27 studies, 3 included children between 2 to 17 years (Supplemental Refs 7,13,21). **Table 3** shows the characteristics of the studies included in this review.

FH SCREENING TOOLS. The screening tools identified in the review differed in terms of methodology, FH diagnostic criteria (reference standard), and implementation settings. Study populations also varied from patients from general practice and community cohorts to specialized populations, such as patients undergoing coronary angiography, FH screening programs, and lipid clinics. Three methods were used to develop the screening tools:

TABLE 3 Characteristics of Selected Studies

Study ID	First Author (Year)	Title	Country of Study Population	Study Design	Study Population
1	Gidding et al (2023)	Yield of Familial Hypercholesterolemia Genetic and Phenotypic Diagnoses After Electronic Health Record and Genomic Data Screening.	United States	Diagnostic test accuracy study	Adults
2	Gratton et al (2023)	A machine learning model to aid detection of familial hypercholesterolaemia	United Kingdom	Diagnostic test accuracy study	Adults
3	Hesse et al (2022)	Familial Hypercholesterolemia Identification by Machine Learning Using Lipid Profile Data Performs as Well as Clinical Diagnostic Criteria.	South Africa	Diagnostic test accuracy study	Adults
4	Wang et al (2022)	Developing a Hybrid Risk Assessment Tool for Familial Hypercholesterolemia: A Machine Learning Study of Chinese Arteriosclerotic Cardiovascular Disease Patients.	China	Diagnostic test accuracy study	Adults
5	Silva et al (2022)	Introducing genetic testing with case finding for familial hypercholesterolaemia in primary care: qualitative study of patient and health professional experience.	United Kingdom	Qualitative study of patient and health professional experience.	Adults
6	Jones et al (2022)	Cost-Effectiveness of Screening Algorithms for Familial Hypercholesterolaemia in Primary Care.	United Kingdom	Cost-effectiveness study	Adults
7	Albuquerque et al (2022)	Performance comparison of different classification algorithms applied to the diagnosis of familial hypercholesterolemia in paediatric subjects.	Portugal	Diagnostic test accuracy study	Children
8	Mohammadnia et al (2022)	Electronic health record-based facilitation of familial hypercholesterolaemia detection sensitivity of different algorithms in genetically confirmed patients	the Netherlands	Diagnostic test accuracy study	Adults
9	Qureshi et al (2021)	Comparing the performance of the novel FAMCAT algorithms and established case-finding criteria for familial hypercholesterolaemia in primary care.	United Kingdom	Diagnostic test accuracy study	Adults
10	Jones et al (2021)	Acceptability, Appropriateness, and Feasibility of Automated Screening Approaches and Family Communication Methods for Identification of Familial Hypercholesterolemia: Stakeholder Engagement Results from the IMPACT-FH Study.	United States	Qualitative study of patient and health professional experience.	Adults
11	Sheth et al (2021)	Implementation of a Machine-Learning Algorithm in the Electronic Health Record for Targeted Screening for Familial Hypercholesterolemia: A Quality Improvement Study.	United States	Diagnostic test accuracy study	Adults
12	Carvalho et al (2021)	Application of a risk stratification tool for familial hypercholesterolaemia in primary care: an observational cross-sectional study in an unselected urban population.	United Kingdom	Diagnostic test accuracy study	Adults
13	Correia et al (2021)	Machine learning modelling of blood lipid biomarkers in familial hypercholesterolaemia versus polygenic/ environmental dyslipidaemia.	Portugal	Diagnostic test accuracy study	Children
14	Tada et al (2021)	Clinical diagnostic criteria of familial hypercholesterolemia - A comparison of the Japan atherosclerosis society and Dutch lipid clinic network criteria.	Japan	Diagnostic test accuracy study	Adults
15	Akyea et al (2020a)	Evaluating a clinical tool (FAMCAT) for identifying familial hypercholesterolaemia in primary care: a retrospective cohort study.	United Kingdom	Diagnostic test accuracy study	Adults
16	Akyea et al (2020b)	Performance and clinical utility of supervised machine-learning approaches in detecting familial hypercholesterolaemia in primary care.	United Kingdom	Diagnostic test accuracy study	Adults
17	Pina et al (2020)	Virtual genetic diagnosis for familial hypercholesterolemia powered by machine learning.	Italy Sweden	Diagnostic test accuracy study	Adults
18	Myers et al (2019)	Precision screening for familial hypercholesterolaemia: a machine learning study applied to electronic health encounter data.	United States	Diagnostic test accuracy study	Adults
19	Sun et al (2019)	A modified algorithm with lipoprotein(a) added for diagnosis of familial hypercholesterolemia.	China	Diagnostic test accuracy study	Adults
20	Weng et al (2019)	Detection of familial hypercholesterolaemia: external validation of the FAMCAT clinical case-finding algorithm to identify patients in primary care.	United Kingdom	Diagnostic test accuracy study	Adults
21	Banda et al (2019)	Finding missed cases of familial hypercholesterolemia in health systems using machine learning.	United States	Diagnostic test accuracy study	Children/Adults
22	Cao et al (2019)	A Novel Modified System of Simplified Chinese Criteria for Familial Hypercholesterolemia (SCCFH).	China	Diagnostic test accuracy study	Adults

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TABLE 3 Continued

Study ID	First Author (Year)	Title	Country of Study Population	Study Design	Study Population
23	Ruel et al (2018)	Simplified Canadian Definition for Familial Hypercholesterolemia.	Canada Australia	Diagnostic test accuracy study	Adults
24	Besseling et al (2017)	Selection of individuals for genetic testing for familial hypercholesterolaemia: development and external validation of a prediction model for the presence of a mutation causing familial hypercholesterolaemia.	the Netherlands	Diagnostic test accuracy study	Adults
25	Troeung et al (2016)	A new electronic screening tool for identifying risk of familial hypercholesterolaemia in general practice	Australia	Diagnostic test accuracy study/ Cost-effectiveness study	Adults
26	Safarova et al (2016)	Rapid identification of familial hypercholesterolemia from electronic health records: The SEARCH study.	United States	Diagnostic test accuracy study	Adults
27	Weng et al (2015)	Improving identification of familial hypercholesterolaemia in primary care: derivation and validation of the familial hypercholesterolaemia case ascertainment tool (FAMCAT).	United Kingdom	Diagnostic test accuracy study	Adults

References for all author groups mentioned in this table are included in Supplemental Table 2.

multivariable logistic regression (LR), simplified clinical diagnostic criteria, and ML models (Table 4).

Patients with homozygous FH and secondary causes of hypercholesterolemia like severe or untreated hypothyroidism, nephrotic syndrome, and liver diseases were excluded from the training data sets to ensure homogeneity of the study population and robustness of the algorithms. Sex, age, lipid levels (both treated and untreated), lipid-lowering medications, and a personal or family history of ASCVD were among the predictors that were consistent in most of the models. Algorithms derived from ML models employed several types of ML techniques, with random forest, ML-based LR, and ensemble learning being the most utilized methods (Table 4). While some tools were derived from a combination of multiple ML models, others such as FIND FH utilized a single ML method.

TABLE 4 Methods/Techniques Used in Deriving FH Screening Tools

Methods/Techniques	Number of Screening Tools
Machine learning techniques	
Random forest	3
Logistic regression[a]	5
Ensemble learning	3
Gradient boosting machine	3
Neural network	3
Decision tree	3
Deep learning	2
Naive Bayes	1
Classification tree	1
Lasso regression	1
Established multivariate analysis	
Multivariable logistic regression[b]	3
Other	
Simplified clinical diagnostic criteria[c]	5

[a]This is a machine learning-based logistic regression model. [b]This is the standard multivariable logistic regression used in the field of statistics. [c]This covers modified diagnostic criteria other than the traditional criteria including the Dutch Lipid Clinic Network (DLCN) criteria, Simon Broome diagnostic (SB) criteria, and Make Early Diagnosis to Prevent Early Death (MEDPED) criteria.

PERFORMANCE OF SCREENING TOOLS: CLINICAL VALIDITY. The performance of these tools was assessed based on the reported sensitivity, specificity, PPV, and NPV. Four different FH diagnostic criteria were used as reference standards to estimate the performance metrics: incident FH diagnosis coded in health records, genetic diagnosis, DLCN, and the SB criteria. In the majority of studies that used reference standards other than traditional criteria (DLCN, SB), the performance metrics were better in the novel screening tools than in the traditional tools. Most of the novel screening tools showed robust evidence of clinical validity, with variable sensitivity (12% to 100%), specificity (60% to 100%), PPV (0.68% to 100%), and NPV (73% to 100%) (Table 5). These estimates were based on varying probability thresholds of population prevalence of FH as shown in Table 5. The Familial Hypercholesterolemia Case Ascertainment Tool (FAMCAT) (1 & 2) and FIND FH algorithms were the most frequently validated screening tools in most of the reviewed studies. Both algorithms consistently demonstrated good performance in FH detection in most of the study cohorts (Table 5).

TABLE 5 Summary of the Clinical Validity of Common FH Screening Algorithms Derived From Electronic Health Records

Model	Method Used	Country of Origin	Component of Model	Study Population	Summary of Performance Metrics	Summary of Other Findings
FAMCAT 1	Multivariable logistic regression	United Kingdom	1. Sex 2. Age 3. Highest cholesterol measurement recorded 4. Triglycerides within 1 month of highest measurement 5. Lipid-lowering drugs used within 1 month of 3 6. Family history of FH 7. Family history of MI 8. Family history of raised cholesterol 9. Type 1 or 2 DM 10. CKD	Primary care patients from general practice	**Weng 2015** (n = 2,971,562; CPRD data set): Reference standard: incident FH diagnosis coded in health records. number of FH cases = 5,050 AUC: • **FAMCAT1: 0.860 (95% CI: 0.848-0.871)** • SB criteria: 0.749 (0.735, 0.763) • DLCN: 0.737 (0.723, 0.752), • Cholesterol criteria: 0.556 (0.527, 0.587). Other performance metric for FAMCAT1 at a prevalence of 1 in 500: • Sensitivity: 70% • Specificity: 88%	
					Weng 2019 (n = 747,000; QResearch database): Reference standard: incident FH diagnosis coded in health records. Number of FH cases = 1,219 AUC: • **FAMCAT1: 0.832 (0.820, 0.845)** • SB criteria: 0.694 (0.681, 0.703) • DLCN: 0.724 (0.710, 0.738) • MEDPED: 0.624 (0.609, 0.638) • Cholesterol criteria: 0.556 (0.527, 0.587). Other performance metric for FAMCAT1 at a prevalence of 1 in 500: • Sensitivity: 84% • Specificity: 60% • PPV: 0.84% • NPV: 99.2% prevalence of 1 in 250: • Sensitivity: 72% • Specificity: 84% • PPV: 1.8% • NPV: 98.2%	In the highest decile of predicted probability, 752 cases were observed and 638 were predicted. Performance of FAMCAT1 among ethnic groups: AUC: • White, White British, or other White: 0.831 (0.816, 0.847) • Asian, Asian British, or other Asian: 0.767 (0.638, 0.905) • Black, Black British, African, or Caribbean: 0.850 (0.759, 0.942) • Mixed or multiple ethnic groups: 0.887 (0.827, 0.947) • Other ethnic groups: 0.809 (0.728, 0.891) • Unknown ethnicity- 0.832 (0.808, 0.855)
					Akyea 2020 (n = 1,030,183; RCGP data set): Reference standard: incident FH diagnosis coded in health records Number of FH case = 1,707 AUC: • **FAMCAT1: 0.844 (0.834, 0.854)** • FAMCAT2: 0.894 (0.885, 0.903) • SB criteria: 0.730 (0.719, 0.741) • DLCN: 0.766 (0.755, 0.778) At a probability cutoff of 1 in 250 FAMCAT1 had • Sensitivity: 77.5% (75.4, 79.5) • Specificity: 81.1% (81.0, 81.2) • PPV: 0.68% (0.64, 0.71) • NPV: 100%	

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TABLE 5 Continued

Model	Method Used	Country of Origin	Component of Model	Study Population	Summary of Performance Metrics	Summary of Other Findings
					Carvalho 2021 (n = 777,128): FAMCAT1 was used to estimate FH risk/diagnosis. • At a probability threshold of 1 in 250, FAMCAT1 risk score identified 11,736 (1.5%) as likely FH cases • At a probability threshold of 1 in 500, FAMCAT1 risk score identified 23,798 (3.1%) as likely FH cases • Additionally, when the algorithm was applied to individuals with ischemic heart disease, the estimated prevalence of likely FH cases increased significantly (6.9%-11.8%). **Qureshi 2021** (n = 260): Reference standard: genetic diagnosis (NGS) Number of FH cases: 16 AUC: • **FAMCAT1 (at 0.140 threshold): 0.63 (0.51, 0.75)** • FAMCAT2 (at 0.0047 threshold): 0.82 (0.70, 0.94) • SB possible FH: 0.64 (0.51, 0.76) • DLCN score ≥6: 0.66 (0.54, 0.79) • Cholesterol threshold: 0.68 (0.56, 0.81) Sensitivity: • **FAMCAT1 (at 0.140 threshold): 31.2% (11.0, 58.7)** • FAMCAT2 (at 0.0047 threshold): 68.8% (41.3, 89.0) • SB possible FH: 56.3% (29.9, 80.2) • DLCN score ≥6: 37.5% (15.2, 64.6) • Cholesterol threshold: 43.8% (19.8, 70.1) Specificity: • **FAMCAT1 (at 0.140 threshold): 94.7% (91.1, 97.1)** • FAMCAT2 (at 0.0047 threshold): 94.7% (91.1, 97.1) • SB possible FH: 70.9% (64.8, 76.5) • DLCN score ≥6: 95.5% (92.1, 97.7) • Cholesterol threshold: 92.6% (88.6, 95.6) PPV, using an FH prevalence of 0.056: • **FAMCAT1 (at 0.140 threshold): 25.8% (12.8, 45.2)** • FAMCAT2 (at 0.0047 threshold): 43.4% (28.3, 57.4) • SB possible FH: 10.3% (6.7, 15.3) • DLCN score ≥6: 33.0% (17.5, 52.5) • Cholesterol threshold: 26.0% (14.8, 40.9)	

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TABLE 5 Continued

Model	Method Used	Country of Origin	Component of Model	Study Population	Summary of Performance Metrics	Summary of Other Findings
					NPV, using an FH prevalence of 0.056: • **FAMCAT1 (at 0.140 threshold): 95.9% (94.4, 97.0)** • FAMCAT2 (at 0.0047 threshold): 98.1% (96.1, 99.0) • SB possible FH: 96.5% (94.0, 97.9) • DLCN score ≥6: 96.3% (94.7, 97.4) • Cholesterol threshold: 96.5% (94.8, 97.7)	
FAMCAT 2	Multivariable logistic regression	United Kingdom	1. Sex 2. Age 3. Highest cholesterol measurement recorded (fitted as a continuous variable) 4. Triglycerides within 1 month of highest measurement (fitted as a continuous variable) 5. Lipid-lowering drugs used within 1 month of 3 6. Family history of FH 7. Family history of MI 8. Family history of raised cholesterol 9. Type 1 or 2 DM 10. CKD 11. Personal history of premature MI 12. History of PVD	Primary care patients from general practice	**Akyea 2020** (n = 1,030,183; RCGP data set): Reference standard: FH diagnosis coded in EHR Number of FH case = 1,707 AUC: • **FAMCAT2: 0.894 (0.885, 0.903)** • FAMCAT1: 0.844 (0.834, 0.854) • SB criteria: 0.730 (0.719, 0.741) • DLCN: 0.766 (0.755, 0.778) At a probability cutoff of 1 in 250 FAMCAT2 had, • Sensitivity: 69.4% (67.2, 71.6) • Specificity: 92.8% (92.8,92.9) • PPV: 1.58% (1.49, 1.67) • NPV: 100% **Qureshi 2021** (n = 260): Reference standard: genetic diagnosis (NGS) Number of FH cases: 16 AUC: • **FAMCAT2 (at 0.0047 threshold): 0.82 (0.70, 0.94)** • FAMCAT1 (at 0.140 threshold): 0.63 (0.51, 0.75) • SB possible FH: 0.64 (0.51, 0.76) • DLCN score ≥6: 0.66 (0.54, 0.79) • Cholesterol threshold: 0.68 (0.56, 0.81) Sensitivity: • **FAMCAT2 (at 0.0047 threshold): 68.8% (41.3, 89.0)** • FAMCAT1 (at 0.140 threshold): 31.2% (11.0, 58.7) • SB possible FH: 56.3% (29.9, 80.2) • DLCN score ≥6: 37.5% (15.2, 64.6) • Cholesterol threshold: 43.8% (19.8, 70.1)	

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TABLE 5 Continued

Model	Method Used	Country of Origin	Component of Model	Study Population	Summary of Performance Metrics	Summary of Other Findings
					Specificity: • **FAMCAT2 (at 0.0047 threshold): 94.7% (91.1, 97.1)** • FAMCAT1 (at 0.140 threshold): 94.7% (91.1, 97.1) • SB possible FH: 70.9% (64.8, 76.5) • DLCN score ≥6: 95.5% (92.1, 97.7) • Cholesterol threshold: 92.6% (88.6, 95.6) PPV, using an FH prevalence of 0.056: • **FAMCAT2 (at 0.0047 threshold): 43.4% (28.3, 57.4)** • FAMCAT1 (at 0.140 threshold): 25.8% (12.8, 45.2) • SB possible FH: 10.3% (6.7, 15.3) • DLCN score ≥6: 33.0% (17.5, 52.5) • Cholesterol threshold: 26.0% (14.8, 40.9) NPV, using an FH prevalence of 0.056: • **FAMCAT2 (at 0.0047 threshold): 98.1% (96.1, 99.0)** • FAMCAT1 (at 0.140 threshold): 95.9% (94.4, 97.0) • SB possible FH: 96.5% (94.0, 97.9) • DLCN score ≥6: 96.3% (94.7, 97.4) • Cholesterol threshold: 96.5% (94.8, 97.7)	
					Mohammadnia 2022 (n = 208 genetically confirmed FH patients) Sensitivity of models at the time of genetic confirmation of FH (T1) using EHR data: • DLCN score ≥6: 19% (14, 25) • **FAMCAT2: 74% (67, 79)** Sensitivity of models during the first visit (T2) using EHR data: • DLCN score ≥6: 22% (17-28) • **FAMCAT2: 32% (26, 39)** Sensitivity of models at the time of genetic confirmation of FH (T1) using all data: • DLCN score ≥6: 26% (20, 32) • **FAMCAT2: 81% (75, 86)** • MEDPED: 31% (25, 37) • SB: 17% (13, 23) Sensitivity of models during the first visit (T2) using all data: • DLCN score ≥6: 28% (22-34) • **FAMCAT2: 45% (39, 52)** • MEDPED: 11% (7, 15) • SB: 15% (11, 21)	

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TABLE 5 Continued

Model	Method Used	Country of Origin	Component of Model	Study Population	Summary of Performance Metrics	Summary of Other Findings
FAMCAT ML	Supervised ML models • ML-based logistic regression • Random forest • Gradient boosting • Deep learning • Ensemble	United Kingdom	Top predictors in the models: Highest total cholesterol, triglycerides at highest total cholesterol, age at highest total cholesterol, hypertension control at highest total cholesterol, liver disease at highest total cholesterol, highest LDL-C, triglycerides at highest LDL-C, age at highest LDL-C, systolic BP at highest LDL-C, hypothyroidism control at highest LDL-C, kidney disease at highest LDL-C, family history of FH, family history of all CHD, family, history of premature CHD, sex, any diagnosis of CHD, BMI, statin potency at baseline, tendon xanthoma, any diagnosis of diabetes ever.	Primary care patients from general practice	**Akyea 2020**b (n = 4, 027,775; CPRD data set): Reference standard: incident FH diagnosis coded in health records Number of FH case = 7,928 AUC: • ML-based logistic regression: 0.812 • Random forest: 0.891 • Gradient boosting: 0.892 • Deep learning: 0.892 • Ensemble: 0.890 Other performance metric at a prevalence of 1 in 250: Sensitivity: • ML-based logistic regression: 37.6% (35.5, 39.8) • Random forest: 69.1% (67.0, 71.2) • Gradient boosting: 58.3% (56.1, 60.5) • Deep learning: 72.6% (70.6, 74.6) • Ensemble: 30.5% (28.4, 32.6) Specificity: • ML-based logistic regression: 96.7% (96.6, 96.7) • Random forest: 92.0% (92.0, 92.1) • Gradient boosting: 95.8% (95.8, 95.9) • Deep learning: 90.0% (89.9, 90.0) • Ensemble: 99.3% (99.3, 99.3) PPV: • ML-based logistic regression: 4.4% (4.1, 4.6) • Random forest: 3.4% (3.3, 3.5) • Gradient boosting: 5.3% (5.1, 5.5) • Deep learning: 2.8% (2.8, 2.9) • Ensemble: 15.5% (14.5, 16.4) NPV: • ML-based logistic regression: 99.7% (99.7, 99.8) • Random forest: 99.9% (99.9, 99.9) • Gradient boosting: 99.8% (99.8, 99.8) • Deep learning: 99.9% (99.9, 99.9) • Ensemble: 99.7% (99.7, 99.7	% high probability/probable FH cases identified by models: • ML-based logistic regression: 3.38 • Random forest: 8.09 • Gradient boosting: 4.27 • Deep-learning: 10.16 • Ensemble: 0.73 Although the ensemble model could identify 0.73% (the least among the 5 models) of the population as probable FH cases requiring clinical review, it had the highest PPV (15.5%) and positive likelihood ratio (45.5%). These diagnostic characteristics make the use of the ensemble model more appropriate given resource implications and workload.

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PERFORMANCE OF SCREENING TOOLS: UTILITY. Three of the 27 studies demonstrated evidence of utility (Supplemental Refs 6,16,25). Troeung et al concluded that screening patients from general practice with TARB-Ex is a time- and cost-effective method of identifying individuals suspected to have FH, compared to manual review by a general practitioner (Supplemental Ref 25). In the other 2 studies, the utility of FAMCAT (1, 2, or ML) was assessed either through a cost-effectiveness analysis or by likelihood

TABLE 5 Continued

Model	Method Used	Country of Origin	Component of Model	Study Population	Summary of Performance Metrics	Summary of Other Findings
Mayo SEARCH ePhenotyping algorithm	Clinical criteria with natural language processing component	United States	Modified DLCN criteria using both structured and unstructured EHR data; 1. Family history of hypercholesterolemia or premature ASCVD 2. Personal history of hypercholesterolemia or premature ASCVD 3. Features of FH on physical examination 4. Plasma LDL-C levels	Primary care patients	**Safarova 2016** (n = 131,000): Reference standard: DLCN criteria Number of FH cases: 423 Performance metrics after blinded expert review of 105 randomly selected algorithm derived cases, using a prevalence of 1 in 310: Sensitivity: 97% Specificity: 94% PPV: 94% NPV: 97%	However, when compared to the gold standard, the algorithm misclassified 19 individuals. Specifically, the DLCN score was overestimated in 13 patients and underestimated in 6 patients. Additionally, 5 patients were reclassified from definite/probable FH to possible FH, while only one patient was incorrectly grouped as possible FH despite having a probable FH diagnosis.
					Gidding 2023[7] (n = 59,729): Reference standard: genetic diagnosis (P/LP variants using NGS) and phenotypic diagnosis using DLCN Number of FH cases: 280 Performance metrics using genetic diagnosis as standard Sensitivity: • **Mayo SEARCH: 69.3%** • FIND FH: 12.1% • Mayo of FIND FH: 70.4% Specificity: • **Mayo SEARCH: 82.8%** • FIND FH: 99.1% • Mayo of FIND FH: 82.4% PPV: • **Mayo SEARCH: 1.9%** • FIND FH: 5.9% • Mayo of FIND FH: 1.8% NPV: • **Mayo SEARCH: 99.8%** • FIND FH: 98.6% • Mayo of FIND FH: 99.8%	Mayo SEARCH algorithm flagged 10,415 as likely FH cases, 195 (1.9%) had a P/LP variant for FH. FIND FH identified 573 as likely FH cases, 34 (5.9%) had a P/LP variant for FH. Overall, 197 (70%) of the 280 with P/LP variant were identified by at least 1 algorithm. Phenotypic diagnosis was rarely ascertained due to missing data.
FIND FH	Machine learning model • Random forest	United States	Demographic: Age, sex Conditional: High LDL cholesterol with no lipid-lowering therapies, high LDL cholesterol with high-intensity statin prescription, high LDL cholesterol with moderate-intensity statin prescription, high LDL cholesterol with statins and ezetimibe Prescription based: Total number of prescription codes, number of atorvastatin prescriptions, number of rosuvastatin prescriptions, number of evolocumab prescriptions. Diagnosis based: Number of E78.00 codes (hypercholesterolaemia), total number of diagnosis codes, number of E78.4 or E78.5 codes (hyperlipidemia), number of I10 codes (hypertension). Procedure based: Total number of procedure codes, number of 93,000 codes (electrocardiogram), number of 99,214 codes (outpatient services), number of 36,415 codes (venipuncture) Laboratory result based:	Primary care patients including pediatric population	**Banda 2019** (n = 12,253): Reference standard: genetic testing/clinical diagnosis Number of FH cases: 663 Performance metric for internal validation (prevalence of 1 in 30): • AUC: 0.94 • AUPRC: 0.71 • Sensitivity: 0.75 • Specificity: 0.99 • PPV: 0.88 • F1 score: 0.81 Performance metric for external validation (prevalence of 1 in 70): • AUC: 0.94 • AUPRC: 0.68 • Sensitivity: 0.68 • Specificity: 0.99 • PPV: 0.85 • F1 score: 0.75	The model identified 56 individuals with a high probability of FH. Of the 56 predictions, 39 had a DLCN score of 3-5 (5 of these met MEDPED criteria); 7 had a DLCN score of 6-8 (3 of these met MEDPED criteria); and 1 had a DLCN score >8. ie, 47/56 (84%) had a DLCN score of ≥3 or were MEDPED positive.
					Myers 2019 (n = 170,674,009): Reference standard: genetic testing/clinical diagnosis Number of FH cases: 939 (out of 84,075, training data set) Performance metric using a prevalence of 1 in 71;	FIND FH identified 1,331,759 individuals as likely FH cases among a population of 170,416,201 Americans. In a subset review of 45 of these likely FH cases, 87% were confirmed to have possible, probable, or definite FH by at least one diagnostic criterion or attending physician.

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TABLE 5 Continued

Model	Method Used	Country of Origin	Component of Model	Study Population	Summary of Performance Metrics	Summary of Other Findings
			Maximum value of total cholesterol, maximum value of LDL cholesterol, average value of LDL cholesterol, average value of total cholesterol		• AUC: 0.89 • AUPRC: 0.55 • Sensitivity: 0.45 • PPV: 0.85	Further application of the screening tool to a health care delivery system data set, encompassing structured EHR data from over 170,000 individuals, flagged 866 patients as likely FH cases. Upon review of 103 of these likely FH cases, 77% were confirmed to have possible, probable, or definite FH by at least one diagnostic criterion or an FH expert.
					Sheth 2021[32] (n = 1,607,606): Reference standard: genetic testing (NGS)/clinical diagnosis Using the algorithm, 8614 individuals were flagged as likely FH among the 1,607,606 eligible patients.	Subsequently, 153 patients were seen in the preventive cardiology clinic. Among these patients, 46 were diagnosed with FH based on physician assessment, DLCN or MEDPED criteria, or the presence of an FH mutation. 112 out of the 153 were tested. 16 out of the 112 tested positive for FH after genetic testing, confirming the genetic basis of the disease and 42 patients received an FH diagnosis based on clinical assessment or diagnostic criteria. With the DLCN or MEDPED criteria only, 23 out of the 46 genetically confirmed patients would have been classified as possible FH
					Gidding 2023[7] (n = 59,729): Reference standard: genetic diagnosis (P/LP variants using NGS) and phenotypic diagnosis using DLCN Number of FH cases: 280 Performance metrics using genetic diagnosis as standard Sensitivity: • Mayo SEARCH: 69.3% • **FIND FH: 12.1%** • Mayo of FIND FH: 70.4% Specificity: • Mayo SEARCH: 82.8% • **FIND FH: 99.1%** • Mayo of FIND FH: 82.4% PPV: • Mayo SEARCH: 1.9% • **FIND FH: 5.9%** • Mayo of FIND FH: 1.8% NPV: • Mayo SEARCH: 99.8% • **FIND FH: 98.6%** • Mayo of FIND FH: 99.8%	
Simplified Canadian FH algorithm	Simplified clinical diagnostic criteria	Canada Australia	1. LDL-C levels (≥4.0 mmol/L for men and women younger than 18 years, ≥4.5 mmol/L for ages 18-39 years, and ≥5.0 mmol/L for subjects 40 years of age and older)	1. Patients from a lipidology unit in Canada 2. Patients from an FH	**Ruel 2018** (n = 5,987 for Canada, 947 for Australia); The Canadian model was compared to the SB and DLCN criteria in 2 different cohorts (Canadian and Australian).	

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TABLE 5 Continued

Model	Method Used	Country of Origin	Component of Model	Study Population	Summary of Performance Metrics	Summary of Other Findings
			2. Major criteria: a. FH causing mutation b. LDL-C ≥8.5 mmol/L c. Presence of tendon xanthomas. 3. Minor criteria: a. Family history of elevated LDL-C>95th percentile, according to the LDL-C criteria b. History of ASCVD in the proband or in a first-degree relative younger than 55 years for men or younger than 65 years for women.	program in Australia	Reference standard: SB and DLCN criteria Canadian model vs SB (in Canadian cohort): • Sensitivity: 99.7% • Specificity: 98.9% • PPV: 95.3% • NPV: 99.9%. Canadian model vs DLCN (in Canadian cohort): • Sensitivity: 100% • Specificity: 98.8% • PPV: 94.5% • NPV: 100%. Canadian model vs SB (in Australian cohort): • Sensitivity: 99.3% • Specificity: 98.2% • PPV: 96.1% • NPV: 99.7%. Canadian model vs DLCN (in Australian cohort): • Sensitivity: 80.8% • Specificity: 100% • PPV: 100% • NPV: 88.6%.	
Simplified Chinese Criteria for FH (SCCFH)	Simplified clinical diagnostic criteria	China	A definite diagnosis of FH by this model requires at least 2 of the following 3 criteria: 1. Untreated LDL-C ≥4.8 mmol/L; 2. Tendon xanthomas in the proband; 3. FH pathogenic mutation in the LDLR, APOB, or PCSK9 gene. Possible FH diagnosis was defined as: untreated LDL-C ≥ 4.8 mmol/L and the family history of premature CAD (≤55 years for men; ≤60 years for women) or hypercholesterolemia.	Primary care patients	**Cao 2019** (n = 12,921) Using the SCCFH system, 205 (1.59%) were classified as having definite FH, while the DLCN and SB criteria classified 223 (1.73%) and 202 (1.56%) FH cases, respectively. Reference standard: SB and DLCN criteria Performance metric for SCCFH: SCCFH vs SB- • Sensitivity: 100% • Specificity: 99.9% • PPV: 98.5% • NPV: 100%. SCCFH vs DLCN- • Sensitivity: 91.9% • Specificity: 100% • PPV: 100% • NPV: 99.8%.	
Japan Atherosclerosis Society (JAS) FH Criteria	Simplified clinical diagnostic criteria	Japan	A definitive diagnosis of FH by this model requires at least 2 of the following 3 criteria: 1. LDL cholesterol ≥4.65 mmol/L 2. Tendon xanthomas on the dorsal side of the hands, elbows, or knees or the presence of Achilles tendon hypertrophy or xanthoma tuberosum. 3. A family history of FH or premature CAD within second-degree relatives.	Patients with dyslipidemia	**Tada 2021** (n = 680): Reference standard: genetic diagnosis Performance metric Sensitivity: • JAS FH criteria: 0.863 • DLCN criteria: definitive FH 0.520, probable FH 0.691, possible FH 0.971 Specificity: • JAS FH criteria: 0.956 • DLCN criteria: definitive FH 0.982, probable FH 0.929, possible FH 0.717 PPV: • JAS FH criteria: 0.873 • DLCN criteria: definitive FH 0.910, probable FH 0.771, possible FH 0.543 NPV • JAS FH criteria: 0.953 • DLCN criteria: definitive FH 0.855, probable FH 0.897, possible FH 0.986 Positive likelihood ratio: • JAS FH criteria: 19.806 • DLCN criteria: definitive FH 29.178, probable FH 9.699, possible FH 3.431	The JAS FH criteria classified 173 (25.4%) as definite FH cases, and the DLCN criteria classified 100 as definitive-FH patients, 57 as probable-FH patients, and 156 as possible-FH patients. Among those classified as likely FH cases using the JAS FH criteria, 151(87%) had FH genetic mutations. For those classified as non-FH by the JAS FH criteria, 24 (5%) FH mutation-positive patients were found. In contrast, using the DLCN criteria, 91 (91%) of patients were identified as definitive FH cases, 30 (52.6%) of patients identified as probable FH cases, 49 (31.4%) of patients identified as possible FH cases and 5 (1.4%) of patients identified as unlikely FH patients were found to have FH genetic mutations.

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Model	Method Used	Country of Origin	Component of Model	Study Population	Summary of Performance Metrics	Summary of Other Findings
					Negative likelihood ratio: • JAS FH criteria: 0.143 • DLCN criteria: definitive FH 0.489, probable FH 0.332, possible FH 0.040	
Simple prediction model	Multivariable logistic regression	Netherlands	1. Age (square root) 2. Sex 3. History of CVD* 4. Age of first CVD* event 5. Current statin use 6. Levels of LDL-C (square root), high-density lipoprotein cholesterol (HDL-C- log-transformed), and triglycerides (log-transformed) 7. Presence of hypertension 8. Current smoking 9. Current alcohol use * CVD was defined as a history of myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, or ischemic cerebrovascular accident.	Patients from a national cascade screening program and a lipid clinic	**Besseling 2017** (n = 67,309): Reference standard: genetic diagnosis Number of FH cases: 27,603 Performance metrics: AUC: • Development cohort: 85.4% • Validation cohort: 95.4% Calibration slope: • Development cohort: 1.02 • Validation cohort: 1.06 Other performance metrics in the development cohort: Sensitivity: • Cutoff probability of 0.30: 85.3 (85.1-85.5) • Cutoff probability of 0.70: 49.2 (48.9-49.5) Specificity: • Cutoff probability of 0.30: 67.1 (66.9-67.4) • Cutoff probability of 0.70: 94.5 (94.4-94.6) PPV: • Cutoff probability of 0.30: 64.2 (63.9-64.4) • Cutoff probability of 0.70: 86.1 (85.9-86.4) NPV: • Cutoff probability of 0.30: 86.8 (86.7-87.0) • Cutoff probability of 0.70: 73.0 (72.8-73.1)	
Modified DLCN score with Lp(a)	Simplified clinical diagnostic criteria	China	1. Untreated LDL-C 2. Lp(a) 3. Premature CHD 4. Tendon xanthomas 5. Family history of CHD or hypercholesterolemia	Patients undergoing coronary angiography	**Sun 2019** (n = 10,449): Reference standard: DLCN Number of FH cases: 342 Performance metrics: AUC: • Development cohort: 99.1% • Validation cohort: 99.0% Sensitivity: • Development cohort: 85.77% (80.71, 89.71) • Validation cohort: 87.64% (78.55, 93.37) Specificity: • Development cohort: 98.79% (98.52, 99.02) • Validation cohort: 97.93% (97.27, 98.43) PPV: • Development cohort: 70.45% (64.96, 75.43) • Validation cohort: 60.0% (51.02, 68.38) NPV: • Development cohort: 99.52% (99.33, 99.66) • Validation cohort: 99.55% (99.18, 99.76)	

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TABLE 5 Continued

Model	Method Used	Country of Origin	Component of Model	Study Population	Summary of Performance Metrics	Summary of Other Findings
TARB-Ex	Electronic screening using structured query language	Australia	Components of the DLCN criteria A DLCN score ≥5 is considered potential risk patients	Patients from general practice	Troeung 2016 (n = 3,708) Reference standard: Manual review of EMR/DLCN Performance metrics using TARB-Ex: • Sensitivity: 95.5% (77.2% to 99.9%) • Specificity: 96.7% (94.3% to 98.3% • PPV: 65.6% (46.9% to 81.4%) • NPV: 99.7% (98.3% to 100%)	TARB-Ex identified 32 patients with DLCN ≥5 whilst GP manual review identified 22 patients. Using TARB-Ex, screening was completed in 10 min for 360 patients while GP manual review took 60 hours for same number of patients. Notably, TARB-Ex derived higher DLCN scores where the manual review indicated very low FH risk (DLCN ≤3).
Hybrid Risk Assessment Tool for FH	Machine learning model • Stacking ensemble	China	1. LDL-C 2. Premature CHD identified in Taiwan FH diagnostic criteria 3. Family history of premature CHD identified in Taiwan FH diagnostic criteria 4. Family history of premature stroke 5. Premature stroke 6. Premature peripheral vascular disease 7. Tendon xanthomas 8. Age 9. Lipid-lowering medications	Patients with ASCVD	**Wang 2022** (n = 5,597) Reference standard: DLCN Prevalence of FH: 2.57% Performance metric: • AUC: 94.85 (±0.47) • Sensitivity: 97.06% (±0.86) • ACC: ACC of 93.52 (±0.47)	
Fusion/Combined FH model	Machine learning models • ML-based logistic regression • Deep learning • Decision tree	South Africa	1. Age at the time of lipid profile 2. Sex 3. Total cholesterol 4. HDL-C 5. LDL-C 6. Triglycerides Preference was given to results obtained before initiation of lipid-lowering drugs	Patients from lipid clinics	**Hesse 2022** (n = 6,851): Reference standard: genetic diagnosis Number of FH cases: 1,871 Performance metrics of model at an FH prevalence of 64% AUROC: • ML: 71.1% • LDL-C cutoff: 64.2% • DLCN: 70.5% Performance metrics of model at an FH prevalence of 20% AUROC: • ML: 80.1% Performance metrics of model at an FH prevalence of 1% AUROC: • ML: 85.6%	For each selected probability cutoff, the model had the best accuracy and F score in both internal and external data sets.
Machine learning model	Machine learning model – Lasso regression	United Kingdom	1. LDL-C 2. LDL-C x LDL-C 3. LDL-C x statin use 4. Statin use 5. Apo-A1 6. Triglycerides 7. ALT 8. C-reactive protein 9. LDL-C polygenic score (PGS) 10. LDL-C x LDL-C PGS 11. Diastolic BP 12. BMI 13. Prevalent type 2 diabetes 14. Family history of CHD	Population based-cohort (UK Biobank)	**Gratton 2022** (n = 139,779): Reference standard: genetic diagnosis. 488 FH variant carriers were identified. Performance metric: AUC: • Model with PGS for LDL-C: 0.77 (0.71-0.83) • Model without PGS for LDL-C: 0.76 (0.71, 0.82) • Simple model with LDL-C and an indicator for statin prescription: 0.71 (0.65-0.77).	When considering a classification threshold of 0.0013 (0.13%), the model with LDL-C PGS showed the highest net benefit among all the models tested and was able to reduce the number of subjects referred to genetic sequencing.
Machine learning model[a]	Machine learning classification models – • ML-based logistic regression • Decision tree • Random forest • Naïve Bayes	Portugal	1. LDL-C 2. Triglycerides 3. Apo-A1 4. BMI 5. Sex 6. Lp(a)	Children (aged 2-17 years) from a population based-cohort (Portuguese FH study)	**Albuquerque 2022** (n = 286): Reference standard: genetic diagnosis 104 FH variant carriers were identified. Performance metric under cutoff value of 0.5: Acc: • LR: 0.84 • RF: 0.84 • NB: 0.84	

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Model	Method Used	Country of Origin	Component of Model	Study Population	Summary of Performance Metrics	Summary of Other Findings
					Sensitivity: • LR: 0.75 • RF: 0.71 • NB: 0.70 Specificity: • LR: 0.90 • RF: 0.91 • NB: 0.92 PPV: • LR: 0.82 • RF: 0.85 • NB: 0.84 NPV: • LR: 0.86 • RF: 0.84 • NB: 0.84 Performance metric by maximizing Youden index: Acc: • LR: 0.84 • RF: 0.83 • NB: 0.83 Sensitivity: • LR: 0.84 • RF: 0.86 • NB: 0.79 Specificity: • LR: 0.85 • RF: 0.81 • NB: 0.86 PPV: • LR: 0.79 • RF: 0.72 • NB: 0.77 NPV: • LR: 0.90 • RF: 0.91 • NB: 0.88	
Machine learning model[a]	Machine learning classification models – 10 different models	Portugal	1. LDL-C 2. ApoB 3. Apo-AI 4. Triglyceride 5. LDL1 6. ApoC-III 7. Total cholesterol 8. BMI 9. Age 10. HDL-C 11. Apo-AII 12. ApoC-II 13. ApoC-III	Children (aged 2-17 years) from a population based-cohort (Portuguese FH study)	**Correia 2021** (n = 211): Reference standard: genetic diagnosis 88 FH variant carriers were identified. Performance metric for top 10 models; Model 1: Acc-0.84; Sensitivity-0.91; Specificity-0.86; AUC-0.92 Model 2: Acc-0.84; Sensitivity-0.83; Specificity-0.92; AUC-0.91 Model 3: Acc-0.77; Sensitivity-0.82; Specificity-0.90; AUC-0.89 Model 4: Acc-0.77; Sensitivity-0.82; Specificity-0.80; AUC-0.88 Model 5: Acc-0.74; Sensitivity-0.82; Specificity-0.85; AUC-0.88 Model 6: Acc-0.81; Sensitivity-0.82; Specificity-0.85; AUC-0.87 Model 7: Acc-0.77; Sensitivity-0.82; Specificity-0.90; AUC-0.87 Model 8: Acc-0.77; Sensitivity-0.73; Specificity-0.75; AUC-0.76 Model 9: Acc-0.77; Sensitivity-0.91; Specificity-0.60; AUC-0.75 Model 10: Acc-0.85; Sensitivity-0.73; Specificity-0.65; AUC-0.75	

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TABLE 5 Continued

Model	Method Used	Country of Origin	Component of Model	Study Population	Summary of Performance Metrics	Summary of Other Findings
Machine learning model	Machine learning classification models – • Classification tree • Gradient boosting machine • Neural network	Italy Sweden	1. LDL-C/age 2. Triglycerides/LDL-C 3. HDL-C	Patients from lipid clinics	**Pina 2020** (n = 612): Reference standard: genetic diagnosis. 418 FH variant carriers were identified. Performance metric in Gothenburg (Sweden) cohort: AUC: • CT: 0.790 (0.782, 0.799) • GBM: 0.829 (0.820, 0.838) • NN: 0.833 (0.774, 0.910) • DLCN: 0.683 (0.672, 0.693) Sensitivity: • CT: 0.739 (0.711, 0.768) • GBM: 0.732 (0.721, 0.743) • NN: 0.853 (0.756, 0.939) • DLCN: 0.676 (0.066, 0.690) Specificity: • CT: 0.79 (0.767, 0.816) • GBM: 0.813 (0.799, 0.826) • NN: 0.579 (0.390, 0.770) • DLCN: 0.606 (0.594, 0.619) Acc: • CT: 0.766 (0.750, 0.783) • GBM: 0.776 (0.768, 0.785) • NN: 0.794 (0.716, 0.860) • DLCN: 0.636 (0.626, 0.646) PPV: • CT: 0.743 (0.720, 0.766) • GBM: 0.765 (0.752, 0.777) • NN: 0.813 (0.672, 0.936) • DLCN: 0.580 (0.570, 0.590) NPV: • CT: 0.791 (0.772, 0.810) • GBM: 0.790 (0.783, 0.798) • NN: 0.784 (0.667, 0.876) • DLCN: 0.699 (0.688, 0.709)	Performance metric in Milan (Italy) cohort: AUC: • CT: 0.701 (0.702[b], 0.710) • GBM: 0.779 (0.776, 0.784) • NN: 0.762 (0.727, 0.784) • DLCN: 0.64 Sensitivity: • CT: 0.693 (0.678, 0.707) • GBM: 0.726 (0.722, 0.730) • NN: 0.121 (0.061, 0.190) • DLCN: 0.83 Specificity: • CT: 0.693 (0.704[b], 0.763) • GBM: 0.658 (0.645, 0.670) • NN: 0.947 (0.895, 0.982) • DLCN: 0.46 Acc: • CT: 0.70 (0.692, 0.710) • GBM: 0.715 (0.712, 0.719) • NN: 0.818 (0.792, 0.834) • DLCN: 0.77 PPV: • CT: 0.935 (0.929, 0.941) • GBM: 0.920 (0.917, 0.923) • NN: 0.872 (0.857, 0.891) • DLCN: 0.89 NPV: • CT: 0.308 (0.304, 0.313) • GBM: 0.308 (0.304, 0.313) • NN: 0.386 (0.326, 0.445) • DLCN: 0.33

[a]Studies conducted among pediatric subjects only. [b]Value reported as seen in the original paper.

Acc = accuracy; ALT = alanine aminotransferase; ApoB = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; AUC = area under the receiver operating curves; AUPRC = area under the precision-recall curve; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CHD = coronary heart disease; CKD = chronic kidney disease; CPRD = Clinical Practice Research Datalink; CVD = cardiovascular disease; CT = classification tree; DM = diabetes mellitus; DLCN = Dutch Lipid Clinic Network; EMR = electronic medical records; EHR = electronic health record; FH = familial hypercholesterolemia; GBM = gradient boosting machine; HDL-C = high-density lipoprotein cholesterol; NGS = next generation sequencing; MI = myocardial infarction; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein (a); LR = logistic regression; NB = naïve bayes; NN = neural network; NPV = negative predictive value; P/LP = pathogenic/likely pathogenic; PPV = positive predictive value; PVD = peripheral vascular disease; RF = random forest; SB = Simon Broome.

ratios and expected case-review workload. FAMCAT 2 emerged as the preferred screening method in the study by Jones et al, as it was found to be cheaper and effective compared to FAMCAT1, simple cholesterol criteria, SB, and DLCN (Supplemental Ref 6). Akyea et al also found that FAMCAT ML model derived with ensemble learning had the best positive likelihood ratio and was found more appropriate than 4 other ML models (ML-based LR, random forest, gradient boosting, and deep learning) given resource implications and workload (Supplemental Ref 16).

PERFORMANCE OF SCREENING TOOLS IN MINORITY GROUPS AND LOW-RESOURCE SETTINGS. Overall, the representation of racial and ethnic minority groups in the reviewed studies was low. Of the 24 studies focusing on diagnostic test accuracy, only 6 provided information on the racial and ethnic composition of the study populations used for both development and validation of the screening tools. The participation of African American/Black Caribbean/Black African people in these 6 studies ranged from 1.2% to 13.4%, indicating the underrepresentation of this population in the reviewed studies. Hesse et al, the only study conducted in Africa, included only 3.2% Black individuals in the training data set (Supplemental Ref 3). Except for 4 studies conducted among Asian populations, the participation of Asian people in studies conducted outside of Asia varied

from 1.8% to 26%. The performance of FAMCAT1 was specifically evaluated among diverse ethnic groups in Carvalho et al (Supplemental Ref 12) and Weng et al (Supplemental Ref 20). According to Carvalho et al, among patients with ischemic heart disease, the likelihood of FH using the FAMCAT 1 screening tool was highest in White people and lowest in Black people (Supplemental Ref 12). The authors of the study attributed this finding to the lower sensitivity of the FAMCAT 1 screening tool in Black and South Asian ethnic groups. In that same study, the cohort was made up of individuals with high levels of socioeconomic deprivation, relative to UK national averages. For Weng et al, while the predictive accuracy of FAMCAT 1 varied among the ethnic groups examined, overall, the algorithm performed well in these groups (Supplemental Ref 20). Among the qualitative studies included in our review, representation of Black and South Asian adults was limited. For 1 study, Black adults made up only 4.2% and South Asian only 16.6% of the patient population (Supplemental Ref 5).

PATIENT AND HEALTH CARE PROFESSIONALS' EXPERIENCE WITH SCREENING TOOLS. We identified 2 qualitative studies that explored the perspectives of individuals living with FH and health care professionals regarding the use of some of the screening tools identified in this review (Supplemental Refs 5,10). For Silva et al, a diverse group of 24 patients with varying family histories and FH test outcomes along with 17 primary care providers found the FAMCAT tool to be helpful, simple to use, and a good opportunity to enhance CVD prevention (Supplemental Ref 5). In the second qualitative study, individuals with FH (including those who were previously exposed to the FIND FH approach/algorithm) and clinicians with expertise in this field found the algorithm to be feasible, acceptable, and appropriate to identify individuals with FH (Supplemental Ref 10). Study participants viewed the algorithm as a valuable tool for FH detection. Similarly, the health professionals and patients emphasized the importance of addressing the non-familiarity with FH as a potential barrier to the successful implementation of the FIND FH algorithm.

DISCUSSION

We report the first comprehensive evaluation of EHR-based screening tools for FH (**Central Illustration**). The main findings are the wide range of characteristics exhibited by these tools, including sensitivity and specificity, as well as clinically relevant parameters such as PPV and NPV. The variability in the latter may be attributed, in part, to the differing prevalence of FH across populations and health care systems. The heterogeneity among the study cohorts likely impacted the variation in the diagnostic accuracy. Among the screening tools, FAMCAT (1, 2, and ML), FIND FH, Mayo SEARCH, and TARB-Ex had the highest performance metrics for the identification of FH. While FAMCAT (1 and 2) and FIND-FH algorithms were tested across multiple cohorts, Mayo SEARCH and TARB-Ex were used in only 2 and 1 of 27 identified studies, respectively. We found that very few tools other than FAMCAT (1 and 2), FIND FH, Mayo SEARCH, and TARB-Ex have been validated and/or demonstrated strong performance for FH detection. Additionally, our review highlights a paucity of studies evaluating the utility of the identified models for FH detection.

Although the FAMCAT2 and FIND FH algorithms yielded similar performance metrics for the identification of FH, considering the different algorithm components may facilitate an improved understanding for FH detection. FAMCAT 2 was built from the FAMCAT 1 model and includes total cholesterol or LDL-C, age during cholesterol measurement, triglycerides, lipid-lowering drug usage, family history of FH, family history of coronary heart disease, family history of premature coronary heart disease, family history of raised cholesterol, diabetes, and chronic kidney disease (Supplemental Ref 9). In contrast, the FIND FH algorithm includes a combination of demographic (age, race), conditional (eg, high LDL-C with no lipid lowering therapy), prescription (eg, number of atorvastatin prescriptions), diagnosis (eg, number of hypercholesterolemia International Classification of Diseases, Tenth Revision codes), procedure (eg, number of venepunctures), and laboratory (eg, maximum value of LDL-C) (Supplemental Ref 21). Assessing the components of these 2 algorithms suggests that there may not be a 1-size fits all approach to implementing ML approaches within EHRs for identifying probable FH cases and linking such patients to preventive cardiovascular services. Studies that directly compare the performance of these novel tools are lacking, with the notable exception of the Gidding study (Supplemental Ref 1) that applied 2 algorithms, the Mayo SEARCH and the FIND FH algorithms, to the same study population finding improved, but incomplete, case finding. Additionally, there has been

CENTRAL ILLUSTRATION **A Scoping Review of Electronic Health Records-Based Screening Algorithms for Familial Hypercholesterolemia**

OBJECTIVE

To evaluate the performance and utility of existing electronic health record (EHR) based familial hypercholesterolemia (FH) screening algorithms

MAIN FINDINGS

- 14 EHR-based screening tools for FH were identified
- FAMCAT (1, 2, and ML), FIND-FH, Mayo SEARCH , and TARB-Ex had the highest performance metrics for the identificarion of FH
- Evidence supporting the utility of these tools is currently insufficient

FUTURE DIRECTIONS

- Establish universally accepted FH diagnostic criteria to serve as a benchmark for all diagnostic test accuracy studies
- Rigorous evaluation of the utility of these tools to guarantee their effectiveness in real-world healthcare settings
- Diverse and inclusive participation in future research studies could improve the generalizability, equitable adoption, and long-term sustainability of FH screening tools in the general population

Osei J, et al. JACC Adv. 2024;3(12):101297.

a dearth of studies performed for FH algorithms in children. The use of FH algorithms to identify FH cases in childhood has the potential to reduce the risk and severity of ASCVD, as well as facilitate cascade testing.[32-36] However, this would require more frequent lipid testing in children and adolescent beyond what is currently recommended.[37]

We compared ML approaches with established multivariable LR and simplified diagnostic categorization. Although the sample sizes of the studies varied, LR models from multivariable regression models showed better sensitivity and lower specificity when compared with ML models, even with tools like FAMCAT, where both multivariable LR and ML algorithms were utilized in different studies. Despite using relatively fewer predictors, LR models achieved a comparable area under the receiver operating curve when compared to ML algorithms. This aligns with prior research indicating that there was no clear performance advantage of ML over LR in clinical prediction models.[38] Simplified diagnostic criteria, on the other hand, demonstrated strong diagnostic accuracy, albeit based on single studies, and offered a more straightforward method for categorizing patients into likely/unlikely FH groups. However, their validation, implementation, and utility in other populations remain limited. Findings from our study also show that most of the novel EHR-based FH algorithms exhibit superior diagnostic accuracy compared to existing FH tools. Yet, only a few of these tools have demonstrated clear evidence of utility. Important evidence gaps in utility include direct evidence that EHR-based FH algorithms implemented in diverse practice settings and populations effectively align patient management decisions with clinical guidelines and improve health outcomes. Given the need for long-term follow-up care of FH patients after an initial diagnosis, evaluation of the cost-effectiveness of these tools is warranted.

In addition to the test characteristics themselves, the consideration of pretest probability is essential when interpreting clinically relevant characteristics, including PPV and NPV. Pretest probability of FH has

a considerable effect on PPV and NPV performance metrics, which was evident when comparing studies. For example, applying the FAMCAT (1 and 2) and FIND FH algorithms to general population EHR databases yielded very low PPV and high NPV, whereas the opposite was found for the Simplified Canadian FH algorithm applied to lipid clinic patients. Our review further underlines the importance of generating training data sets from samples that have a higher pretest probability of FH, including specialized lipid clinics globally. Future efforts can be focused on creating large data sets derived from lipid clinics across the globe to train a universal FH detection algorithm. However, several current gaps and challenges related to race and socioeconomic status remain among specialized lipid clinics. Systems-level approaches to increase access to specialized lipid care in lower socioeconomic communities should be pursued concurrently with efforts to maximize diagnostic accuracy of FH detection algorithms.

Despite the development of EHR-based screening tools to aid in diagnosing FH cases over the past decade, previous research has highlighted challenges in their implementation into clinical practice.[39] Previous implementation studies have indicated that over half of the patients identified by the FIND FH were either unreachable and/or did not receive responses to their initial requests for further testing.[40,41] Additionally, many patients lack the awareness or education regarding the cardiovascular risk of FH, which hinders their follow-up with genetic testing, even when it is offered free of charge. Furthermore, systems-level barriers, such as privacy policies and reduced access to medical services, make it difficult to reach all identified patients. Lastly, the lack of diversity in training data sets for the EHR-based tools for FH limits the generalizability of the tools to other populations and eventually worsens disparities in CVD care. However, efforts to diversify data, such as testing and implementing FH diagnostic algorithms in blood donor screening programs have been proposed.[42]

STRENGTHS AND LIMITATIONS. This review comprehensively assessed the diagnostic performance and utility of EHR-based screening tools across diverse populations, whereas prior reviews mainly focused on strategies and interventions aimed at improving screening and detection of FH.[39,43,44] Although we adhered to established guidelines and adopted a thorough methodology for conducting and presenting our review, we still acknowledge some limitations to our study. Our search strategy and the decision to include papers published exclusively in English may have resulted in the exclusion of potentially eligible studies. Scoping reviews typically do not include a quality assessment of the included studies. Thus, the assessment of potential biases was not considered in this review. Additionally, the populations among the included studies varied significantly. This limitation precluded us from making meaningful comparisons among these screening tools or assessing their actual impact on FH management.

FUTURE DIRECTIONS. Our findings of reasonable clinical validity and utility of primary care EHR tools for the identification of FH are consistent with current evidence of the potential to improve population-level detection and management of high-risk groups of patients with FH. However, several challenges persist, including inconsistent FH diagnostic criteria and limited representation of racial minority populations and individuals in rural areas. These challenges currently impact our ability to determine the most effective tool for FH detection in different populations and settings. Importantly, although there is no uniform gold standard for EHR-based detection of FH, several ML algorithms have shown promise for improving FH identification, including the FAMCAT (1 and 2), FIND FH, Mayo SEARCH, and TARB-Ex algorithms.

CONCLUSIONS

As we chart the future of EHR-based screening algorithms for FH, further investigation will be needed to address several key areas: establishing universally accepted diagnostic criteria to serve as a benchmark for all diagnostic test accuracy studies, validating and replicating the performance (including model calibration) of current EHR-based screening tools in diverse populations, and evaluating the utility of the existing EHR-based screening tools. Rigorous evaluation of the utility of these tools is needed to guarantee their effectiveness in real-world health care settings. Additionally, objective assessment that compares EHR-based algorithms originating from diverse patient populations to a robust reference standard, in this case, genetic testing using the latest next-generation sequencing, will be informative.

Diverse and inclusive participation in future research endeavors will be essential to improve the generalizability, equitable adoption, and long-term sustainability of FH screening tools in the general population.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: EHR screening tools hold great potential for improving population-level detection and management of patients with FH.

TRANSLATIONAL OUTLOOK: Rigorous evaluation of the utility of EHR-based FH screening tools is needed to ensure their effectiveness in healthcare settings. Additionally, the involvement of diverse populations in future research could improve the generalizability and equitable adoption of the FH tools.

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KEY WORDS **familial hypercholesterolemia, electronic health record, machine learning, performance, utility**

APPENDIX **For supplemental tables please see the online version of this paper.**