American Journal of Preventive Cardiology 21 (2025) 100930

Contents lists available at ScienceDirect

American Journal of Preventive Cardiology

journal homepage: www.journals.elsevier.com/american-journal-of-preventive-cardiology

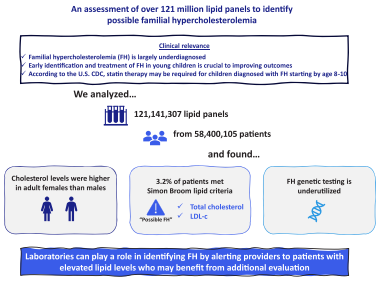
Original Research

A strategy to increase identification of patients with Familial Hypercholesterolemia: Application of the Simon Broome lipid criteria in a large-scale retrospective analysis

James K. Fleming [a,*], Renee M. Sullivan [b], David Alfego [c], Natalia T. Leach [d], Tamara J. Richman [e], Jill Rafalko [a]

[a] Office of the Chief Scientific Officer, Labcorp, 4374 Nire Valley Drive, Burlington, NC 27215, United States
[b] Department of Science and Technology, Labcorp, United States
[c] Center of Excellence for Data Science, AI and Bioinformatics, Labcorp, United States
[d] Molecular Genetics and Cytogenetics, Women's Health and Genetics, Labcorp, United States
[e] Strategic Initiatives Management, Office of the Chief Scientific Officer, Labcorp, United States

GRAPHICAL ABSTRACT



ARTICLE INFO

Keywords:
Hypercholesterolemia
Cholesterol
Low density lipoproteins
Genetic testing
Algorithms
Cardiovascular risk factors
Quality improvement
Mortality

ABSTRACT

Introduction: Familial Hypercholesterolemia (FH) is a primarily autosomal dominant condition characterized by markedly elevated low-density lipoprotein-cholesterol (LDL-c) and an increased risk of atherosclerosis and cardiovascular disease (CVD). Though early identification and treatment are crucial to optimizing outcomes, few laboratory strategies exist to detect FH.

Methods: All lipid tests for total cholesterol (TC) and LDL-c ordered through a large nation-wide network of medical laboratories in the United States (US) from 2018 - 2022 were retrospectively evaluated using a decision tree algorithm based on Simon Broome lipid criteria. If thresholds were met, results were classified as "possible FH" or as "no lipid evidence of FH" if not met.

Results: The review of 121,141,307 lipid panels and associated genetic tests from 58,400,105 patients resulted in 1,843,966 (3.2 %) that were classified as "possible FH". Overall, the mean TC was higher in females than males, particularly in those ≥16 years. LDL-c in the "no lipid evidence of FH" cohort increased year-over-year; LDL-c was stable or decreased in the "possible FH" cohort. Despite the large number of patients classified with "possible FH", very few (0.02 %) matched patients had genetic testing.

* Corresponding author.
E-mail address: fleminj@labcorp.com (J.K. Fleming).

https://doi.org/10.1016/j.ajpc.2025.100930
Received 24 September 2024; Received in revised form 30 December 2024; Accepted 8 January 2025
Available online 9 January 2025

Conclusion: A laboratory-developed algorithm using Simon Broome lipid criteria can help identify patients who may benefit from additional FH evaluation. While critical, testing hyperlipidemic children for FH is grossly underutilized, as is genetic testing for FH. Diagnostic laboratories are uniquely positioned to bring FH to the attention of clinicians, with the goal of earlier diagnosis, cascade testing, and appropriate treatment.

1. Introduction

Familial Hypercholesterolemia (FH) is a common, yet largely underdiagnosed genetic disorder in which LDL-c levels are markedly elevated, significantly increasing the risk of atherosclerosis and CVD. Individuals with FH may exhibit other clinical manifestations associated with excess lipids, including xanthomas, xanthelasmas, and arcus cornealis [1,2]. FH is present from birth and requires early diagnosis to initiate appropriate and timely medical intervention [3]. The American Academy of Pediatrics recommends universal lipid screening for all children 9 to 11 years of age for early detection of FH [4]; aggressive pharmacologic treatment should be undertaken as early as 8 to 10 years of age, or upon diagnosis [3,4].

A variety of algorithms have been proposed for the diagnosis of FH, including but not limited to: Make Early Diagnosis to Prevent Early Death (MEDPED) [5], Dutch Lipid Clinic Network (DLCN) [6], Simon Broome [7], National Lipid Association (NLA) [3], American Heart Association (AHA) [8], Japan Atherosclerosis Society FH Criteria [9], Simplified Canadian Definition for FH [10], and machine learning algorithms based on data from electronic health records [11]. The criteria for diagnosing FH vary according to the algorithm chosen [12], but typically involve one or more of the following: TC or LDL-c levels, clinical presentation, family history, and/or results of genetic testing.

Pathogenic variants in several genes have been shown to affect LDL metabolism and are associated with FH. Variants in the LDL receptor gene (*LDLR*) are most common, accounting for >90 % of cases with an identifiable genetic etiology; variants in apolipoprotein B (*APOB*) and protein convertase subtilisin/kexin type 9 (*PCSK9*) genes account for 5–10 % and <1 % of cases, respectively [13]. *LDLRAP1* mutations are considered rare and lend themselves to a diagnosis of autosomal recessive FH. The presence of a single pathogenic variant in LDLR, APOB, or PCSK9 (heterozygous FH (HeFH)) is the most common presentation; wherein untreated adults typically have significantly elevated TC of 310–580 mg/dL (8–15 mmol/L) and/or elevated LDL-*c* > 190 mg/dL (4.9 mmol/L). Co-occurrence of two pathogenic variants in these genes (homozygous FH (HoFH)) results in a more severe form of FH; these adults have TC values of 460–1160 mg/dL (12–30 mmol/L) with LDL-c values >400 mg/dL (>10.0 mmol/L) [12,14]. A modern-day US based registry of individuals with homozygous FH assessed the presence of xanthomas in 56.3 % of children and 80.4 % of adults. No children had corneal arcus while 46.8 % of adults did [15]. Untreated, individuals with HeFH may die as early as 55–60 years of age while those with HoFH may die before age 20, whereas early diagnosis and effective treatment can avert serious cardiovascular events in later life, barring additional comorbid risk factors [14]. A subset of FH has polygenic etiology due to a cumulative effect of variants in genetic loci associated with LDL-c, and polygenic factors also modulate severity of monogenic FH [16,17]. Not surprisingly, a high prevalence of FH is found in individuals with CVD. FH has been estimated to be 10 times higher in patients with ischemic heart disease (IHD), 20 times higher in patients with premature IHD, and 23 times higher in patients with severe hypercholesterolemia [18].

The prevalence of HeFH was historically cited to be ~1:500 but is now thought to be as high as 1:311, whereas the prevalence of HoFH is estimated at 1:160,000 to 1:400,000 [2,14,18–21]. In the US, it is estimated that fewer than 10 % of individuals with FH receive a diagnosis [11,22]. As there are currently about 1.3 million diagnosed FH cases in the US, it is estimated that >11.5 million Americans have FH, do not know it, and are not being treated appropriately [23].

Although genetic testing is recommended by key professional societies including the American College of Cardiology (ACA) [13], AHA [24], and NLA [25], genetic testing is underutilized in the US with only 3.9 % of diagnosed FH patients listed in the CASCADE-FH registry as tested [22]. Genetic testing as a part of FH cascade screening is also recommended for families where a causative genetic variant has been identified, beginning with first degree relatives, then extending to second- and third-degree relatives [4,12].

In the US, Simon Broome is the most commonly used formal criteria for diagnosing FH [22] and incorporates lipid values, family history, clinical findings and genetic variants to arrive at a diagnosis (Table 1). The lipid criteria separate the clinical decision points for TC and LDL-c based on age, with the pediatric population represented by individuals <16 years of age and the adult population represented by individuals ≥16 years. An individual whose TC and/or LDL-c exceeds a set threshold, and has a genetic mutation in an FH gene, or presents with a personal or family history (first- or second-degree relative) of tendon xanthoma(s) is determined to have “definite” FH. An individual whose TC and/or LDL-c exceeds a set threshold and has a positive family history of premature myocardial infarction (MI), or a family history of elevated total cholesterol is determined to have “possible” FH.

Through employing a unique screening strategy to lipid test results, the current study assessed the prevalence of potential FH in 121,141,307 lipid panels representing a population of over 58 million patients at a large nation-wide medical laboratory. Secondary goals were to examine the utilization of genetic testing in patients meeting FH criteria, and to assess age related trends in lipid and FH testing over a five-year period.

2. Materials and methods

2.1. Analysis of data from lipid panels

Under the conditions of an IRB exemption for de-identification of patient laboratory data from the WCG Western Institutional Review Board (Puyallup, WA), subjects were identified as having any lipid profile or both individual LDL-c and TC orders performed at Labcorp® between January 2018 and December 2022. All lipid analyses were performed using standardized Roche Diagnostics (Indianapolis, IN) reagents and on Roche Diagnostics instrument platforms throughout the Labcorp® network of testing labs. Calculations for LDL-c used the

Table 1
Simon Broome criteria for the diagnosis of familial hypercholesterolemia.

Criteria	Diagnosis
In adults ≥16 years: TC >290 mg/dL (7.5 mmol/L), or LDL-C > 190 mg/dL (4.9 mmol/L) In pediatric patients <16 years: TC >259 mg/dL (6.7 mmol/L), or LDL-C > 155 mg/dL (4.0 mmol/L) AND Tendon xanthoma in the patient or first/second-degree relative, OR alternatively: presence of *LDLR*, *APOB*, or *PCSK9* P/LP variant	Definite
In adults ≥16 years: TC >290 mg/dL (7.5 mmol/L), or LDL-C > 190 mg/dL (4.9 mmol/L) In pediatric patients <16 years: TC >259 mg/dL (6.7 mmol/L), or LDL-C > 155 mg/dL (4.0 mmol/L) AND family history of MI <50 y old in second-degree relative or <60 y old in first-degree relative OR alternatively: family history of TC >7.5 mmol/L (290.0 mg/dL) in a first- or second-degree relative.	Possible

Friedewald formula through 2019 [26] and the Sampson NIH formula [27] beginning in 2020.

Simon Broome criteria was selected as the basis for the FH Lipid Profile due to physician familiarity in the US, as well as demonstrating a higher diagnostic screening yield compared to MEDPED and DLCN FH criteria when used in conjunction with clinical findings [22]. TC and LDL-c levels were compiled and retrospectively evaluated using an internally developed algorithm (FH Lipid Profile Algorithm) (Fig. 1) utilizing Simon Broome lipid criteria as decision points to evaluate for FH If the patient's lipid values exceeded the Simon Broome thresholds, the patient was classified as having "Possible FH"; if values fall below the thresholds, the patient was classified as having "No lipid evidence of FH." It is important to note that only the Simon Broome lipid criteria are used in the algorithm, to the exclusion of clinical presentation or family history, although these are important factors contributing to the diagnosis.

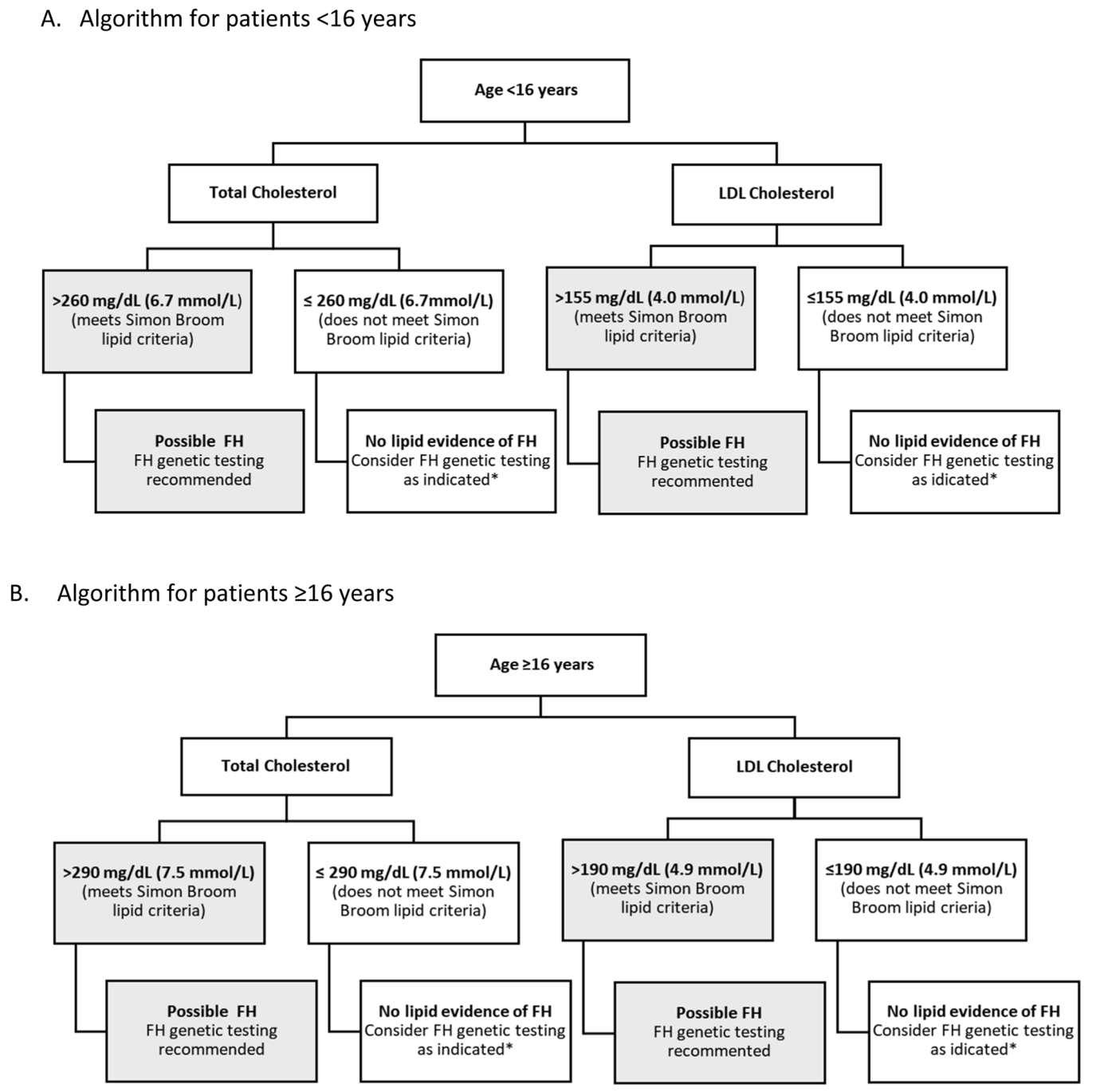


Fig. 1. FH Lipid Profile Algorithm for identification of patients with possible FH from laboratory-based lipid testing. Patients are stratified to the appropriate algorithm by age (A) for age 16 years and (B) for ≥16 years; lipid results are then incorporated with TC and LDL-c decision points based on Simon Broome lipid criteria. If lipid values exceed Simon Broome thresholds, the patient is classified as "possible FH" and FH genetic testing is recommended; if not, the patient is classified as "no lipid evidence of FH" and additional guidance is provided.
Patient Report Statement: *Consider FH genetic testing as indicated, in the presence of clinical manifestations of FH (e.g., arcus cornealis, cutaneous xanthomas); family history of myocardial infarction in 1st degree relatives age 60 or younger, or 2nd degree relatives 50 or younger; or, family history of TC >260 mg/dL in a child, brother or sister <16 years old, or an adult with a TC >290 mg/dL in a 1st or 2nd degree relative.

Patient demographics (Table 2), including age, sex and geographical region, in accord with the US Census designation (Northeast, Midwest, South, West) [28], were summarized by percentages or mean and standard deviation, as applicable, from the total cohort of unique patients; for patients with multiple samples submitted during the study timeframe, demographics and lipid test results were analyzed based on the information associated with the patient's first specimen only. Means were compared using Mann Whitney U testing, with $p < 0.05$ considered significant. Year-over-year trends in lipid results were analyzed using the Mann Kendall Trend test. For the trend analysis, multiple specimens from the same patient were included (e.g., annual testing) in the analysis for the respective year. All statistical analyses were performed with Python 3.7 and the SciPy package. International Classification of Diseases (ICD) codes associated with the laboratory orders were used to assess whether the patient potentially had a diagnosis of, or if there was a suspicion of FH; codes analyzed included: 272.0 (Hypercholesterolemia) for ICD-9, and E78.01 (Familial Hypercholesterolemia) and Z83.42 (Family History of Familial Hypercholesterolemia) for ICD-10.

2.2. Analysis of FH genetic testing

All FH genetic tests performed between January 2018 and December 2023 were cross-referenced with patients that also had lipid testing performed between January 2018 and December 2022 to determine matches based on patient demographics. The timeframe for the analysis of genetic testing results was extended an extra year for comparison to previous years.

Genetic testing for FH includes four genes currently known to be associated with the condition: *APOB, LDLR, LDLRAP1,* and *PCSK9*. Assessment of the *LDLR, LDLRAP1,* and *PCSK9* genes includes sequence analysis of all coding exons and adjacent intron/exon junctions. Assessment of the *APOB* gene is limited to the 556 bp region of exon 26 which harbors the most frequent pathogenic variants. Testing is performed using a hybridization capture method and the Illumina® next-generation sequencing platform. Sequencing reads are aligned to the human genome reference GRCh37/hg19. Variant detection is performed by QIAGEN CLC Genomics and in-house algorithms and does not include copy number variation. Pathogenic (P) and likely pathogenic (LP) variants are reported using numbering and nomenclature recommended by the Human Genome Variation Society [29]. Classification of identified variants is determined by an evidence-based proprietary algorithm in accordance with current American College of Medical Genetics and Genomics and Association for Molecular Pathology (ACMG/AMP) standards [30].

Table 2
Demographic characteristics, lipid results, and genetic testing outcomes in patients tested at Labcorp® between January 2018–December 2022.

		Simon Broome Lipid Criteria Met			Simon Broome Lipid Criteria Not Met		
	All Subjects	All Ages	Age <16 years	Age ≥16 years	All Ages	Age <16 years	Age ≥16 years
N	58,400,105	1843,966	37,900	1806,066	56,556,139	2440,407	54,115,732
Age, yrs. (mean ± SD)	54.8 ± 18.2	54.7 ± 15.0	11.6 ± 3.1	55.6 ± 13.8	54.2 ± 15.6	11.7 ± 3.6	56.1 ± 17.1
Patient Sex							
Female (%)	31,744,519 (54.5 %)	1093,325 (59.3 %)	18,156 (47.9 %)	1075,169 (59.5 %)	30,651,194 (54.2 %)	1219,188 (49.9 %)	29,432,006 (54.4 %)
Male (%)	26,655,586 (45.5 %)	750,641 (40.7 %)	19,744 (52.1 %)	730,897 (40.5 %)	25,904,945 (45.8 %)	1221,219 (50.1 %)	24,683,726 (45.6 %)
Region (%)							
Northeast	8952,045 (15.3 %)	279,345 (15.1 %)	9211 (24.3 %)	270,134 (15.0 %)	8672,700 (15.3 %)	564,072 (23.1 %)	8108,628 (15.0 %)
Midwest	4467,480 (7.6 %)	137,905 (7.5 %)	2405 (6.3 %)	135,500 (7.5 %)	4329,575 (7.7 %)	164,642 (6.7 %)	4164,933 (7.7 %)
South	29,165,792 (49.9 %)	973,078 (52.8 %)	18,658 (49.2 %)	954,420 (52.8 %)	8192,714 (49.8 %)	1159,847 (47.5 %)	27,032,867 (50.0 %)
West	11,654,887 (20.0 %)	359,634 (19.5 %)	6021 (15.9 %)	353,613 (19.6 %)	11,295,253 (20.0 %)	443,946 (18.2 %)	10,851,307 (20.1 %)
Unknown	4159,901 (7.1 %)	94,004 (5.1 %)	1605 (4.2 %)	92,399 (5.1 %)	4065,897 (7.2 %)	107,900 (4.4 %)	3957,997 (7.3 %)
Lipid testing results*							
TC mg/dL, mean ± SD (mmol/L)	181.0 ± 42.3 (4.7 ± 1.1)	297.2 ± 32.7 (7.7 ± 0.8)	252.7 ± 37.7 (6.5 ± 1.0)	298.2 ± 31.9 (7.7 ± 0.8)	177.3 ± 36.4 (4.6 ± 0.9)	154.5 ± 27.1 (4.0 ± 0.7)	181.1 ± 37.2 (4.7 ± 1.0)
LDL mg/dL, mean ± SD (mmol/L)	102.8 ± 35.6 (2.7 ± 0.9)	206.4 ± 29.6 (5.3 ± 0.8)	177.7 ± 34.2 (4.6 ± 0.88)	207.1 ± 29.2 (5.4 ± 0.8)	101.1 ± 30.5 (2.6 ± 0.8)	85.1 ± 23.5 (2.2 ± 0.6)	103.3 ± 32.0 2.7 ± 0.8)
N, with LDL-*c* > 400 mg/dL (10.3 mmol/L)†	2961 (0.005 %)	2961 (0.2 %)	88 (0.2 %)	2873 (0.2 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Genetic testing results at Labcorp® ‡							
Patients with FH genetic + lipid testing (% of total N)	1691 (<0.01 %)	382 (0.02 %)	16 (0.04 %)	366 (0.02 %)	1309 (0.002 %)	20 (0.001 %)	1289 (0.002 %)
Patients with P/LP FH variant + lipid testing (% of row above)	200 (4.0 %)	98 (25.7 %)	9 (56.3 %)	89 (24.3 %)	102 (7.8 %)	1 (5.0 %)	101 (7.8 %)
ICD-9/ICD-10 coding							
Test orders (%) with Family History of FH (Z83.42)	35,877 (0.06 %)	1517 (0.08 %)	328 (0.9 %)	1189 (0.07 %)	34,360 (0.06 %)	6595 (0.3 %)	27,765 (0.05 %)
Test orders (%) with FH (272.0/E78.01)	2090,014 (3.6 %)	105,902 (5.7 %)	1353 (3.6 %)	104,549 (5.8 %)	1984,112 (3.5 %)	12,388 (0.5 %)	1971,724 (3.6 %)

SD= standard deviation.

* For patients with multiple lipid samples submitted during the study timeframe, the results of the patient's first submitted test were used.

† LDL-*c* > 400 is suggestive of HoFH.

‡ For patients that had lipid testing at any time between January 2018 – December 2022 and FH genetic testing at any time between January 2018 – December 2023 at Labcorp®.

3. Results

3.1. Characteristics of the total study population

From January 2018 – December 2022 a total of 121,141,307 lipid panels from 58,400,105 patients were submitted for testing (Table 2). Approximately 55 % of this population was female and 45 % was male. While fewer females than males < 16 years of age are observed to meet the Simon Broome lipid criteria, a significantly higher percentage of females than males meet the criteria after the age of 16. Hormonal homeostasis may be altered in adult females in menstruation, ovulation, pregnancy, and obesity, in addition to resistance to lipid lowering therapy are factors associated with higher lipid level in adult women than in men. The higher incidence of hyperlipidemia along with an emphasis placed on heart disease in women over the past decade within the in the medical literature, lay press, and in programs like the Go Red for Women initiative by the AHA, may be responsible for driving more lipid testing in adult women than men [31–36].

Approximately 97 % of all lipid panels ordered were associated with patients ≥16 years of age, as opposed to 3 % for patients <16 years. Geographically, nearly 50 % of patients tested were from the South, followed by ~20 % from the West, 15 % from the Northeast, and 8 % from the Midwest; geographic location was unknown for 7 % of patients. By region (excluding unknown geography), the South had the highest percentage of patients that met Simon Brome lipid criteria at 3.34 %, followed by the Northeast at 3.12 %, and the West and Midwest, both at 3.09 %. The mean TC in the study population was 181 ± 42 mg/dL (95 % CI: 180.99, 181.01 mg/dL), (4.7 ± 1.1 mmol/L, 95 % CI: 4.70, 4.70 mmol/L), and the mean LDL-c was 103 ± 36 mg/dL (95 % CI: 102.99, 103.01 mg/dL) (2.7 ± 0.9 mmol/L, 95 % CI: 2.70, 2.70 mmol/L), where n = 58,400,105. A total of 3.6 % of patients (2090,014) had testing submitted with an ICD-9 or ICD-10 code indicating Pure/Familial Hypercholesterolemia (i.e., 272.0/E78.01), and an additional 0.06 % (35,877) had testing submitted with an ICD-10 code indicating Family History of FH (i.e., Z83.42).

3.2. Patients classified as "Possible FH" from the FH lipid profile algorithm

Over the 5-year study period, 3.2 % had TC and/or LDL-c levels classified as "Possible FH" from the FH Lipid Profile Algorithm, comprising 37,900 patients <16 years and 1806,066 patients ≥16 years. The mean TC was 253± 38 mg/dL (6.5 ± 1.0 mmol/L) in patients <16 years (95 % CI: 252.32, 253.08 mg/dL or 6.49, 6.51 mmol/L), and 298 ± 32 mg/dL (7.7 ± 0.8 mmol/L) in patients ≥16 years (95 % CI: 298.15, 298.25 mg/dL or 7.69, 7.01 mmol/L). The mean LDL-c was 178 ± 34 mg/dL (4.6 ± 0.9 mmol/L) in patients <16 years (95 % CI: 177.36, 178.04 mg/dL or 4.59, 4.61 mmol/L), and 207 ± 29 mg/dL (5.4 ± 0.8 mmol/L) in patients ≥16 years (95 % CI: 207.06, 207.14 mg/dL or 5.39, 5.40 mmol/L). Further breakdown by smaller age groups and sex can be observed in Supplemental Table 1 for mean TC and LDL-c, and prevalence of meeting Simon Broome lipid criteria in Supplementary Table 2. Approximately 0.2 % (2961) of all patients with "possible FH," had an LDL-c level >400 mg/dL (>10.3 mmol/L), suggestive of HoFH [37]. When patients classified as "Possible FH" were stratified by age and sex (Table 3), mean TC levels were significantly higher in females vs. males in both age groups, however mean LDL-c levels were only higher in females vs. males in the <16 years group. Of note, although statistical significance was reached due to the size of the study, some findings may not be clinically relevant differences.

In 2018, 436,567 of 22,058,067 (2.2 %) of patients were classified as "Possible FH". This percentage steadily increased over the study period, and in 2022, 797,900 of 27,088,064 (2.9 %) patients were classified as "Possible FH". Year-over-year mean TC levels for all patients who met Simon Broome lipid criteria remained relatively stable or trended downward (Fig. 2), though the only statistically significant trend was observed in females <16 years. Similarly, year-over-year mean LDL-c trends for all patients meeting the criteria were also observed to be decreasing (Fig. 3), with statistically significant trends seen in both males and females <16 years.

Table 3
Male and female 5-year mean total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-c) values. For patients with multiple lipid samples submitted during the study timeframe (January 2018 – December 2022), the results of the patient's first submitted specimen were used.

Test	Age	Simon-Broome Lipid Criteria	Male	Female	p-value
TC mean, mg/dL (mmol/L)	< 16 years	Not Met	155.3 (4.0)	156.4 (4.0)	0.0038
	≥16 years	Not Met	171.8 (4.4)	185.5 (4.8)	<0.0001
	< 16 years	Met	254.1 (6.6)	256.7 (6.6)	<0.0243
	≥16 years	Met	295.3 (7.6)	303.9 (7.9)	<0.0001
LDL-c mean, mg/dL (mmol/L)	< 16 years	Not Met	86.7 (2.2)	87.0 (2.2)	0.1701
	≥16 years	Not Met	99.0 (2.6)	104.3 (2.7)	<0.0001
	< 16 years	Met	180.1 (4.7)	181.5 (4.7)	0.0331
	≥16 years	Met	208.8 (5.4)	208.6 (5.4)	1.000

3.3. Patients classified as "No lipid evidence of FH" from the FH lipid profile algorithm

Over the 5-year study period, 56,556,139 of the 58,400,105 patients tested (96.8 %) were classified as "No lipid evidence of FH" from the FH Lipid Profile Algorithm, comprising 2440,407 patients <16 years and 54,115,732 patients ≥ 16 years. The mean TC was 155 ± 27 mg/dL (4.0 ± 0.7 mmol/L) in patients <16 years

(95 % CI: 154.47, 154.53 mg/dL or 3.99, 4.00 mmol/L), and 181 ± 37 mg/dL (4.7 ± 1.0 mmol/L) in patients ≥16 years (95 % CI: 181.09, 181.11 mg/dL or [4.69, 4.70 mmol/L). The mean LDL was 85 ± 24 mg/dL (2.2 ± 0.6 mmol/L) in patients <16 years (95 % CI: 85.07, 85.13 mg/dL or 2.19, 2.20 mmol/L), and 103 ± 32mg/dL (2.7 ± 0.8 mmol/L) in patients ≥16 years (95 % CI: 103.29, 103.31 mg/dL or 2.69, 2.70 mmol/L).

When patients classified as "No lipid evidence of FH" were stratified by age and sex (Table 3), mean TC levels were significantly higher in females vs. males in both age groups. The mean LDL-c levels were significantly higher in females vs. males only in the ≥16 years group. Again, although statistical significance was reached, some differences may not be clinically relevant. Unlike those who met the Simon Broome lipid criteria, the year-over-year mean TC levels for patients not meeting the criteria appeared to trend upward (Fig. 2), though none of these trends were statistically significant. Year-over-year mean LDL-c trends for all patients not meeting the criteria were also observed to be increasing (Fig. 3), with statistically significant increasing trends seen in females <16 years; 84 mg/dL (2.2 mmol/L) in 2018 to 91 mg/dL (2.4 mmol/L) in 2022 and males <16 years; 84 mg/dL (2.2 mmol/L) in 2018 to 90 mg/dL (2.3 mmol/L) in 2022.

3.4. Analysis of FH genetic testing

A broad search of all FH genetic testing performed at Labcorp® from January 2018 - December 2023 (not limited to patients that had lipid testing during the study period) identified a total of 4993 patients tested (Table 4). Of these 4993 patients, 418 (8.4 %) had at least one P or LP variant identified in an FH-associated gene – 411 with a single heterozygous variant, 2 with heterozygous variants identified in more than one

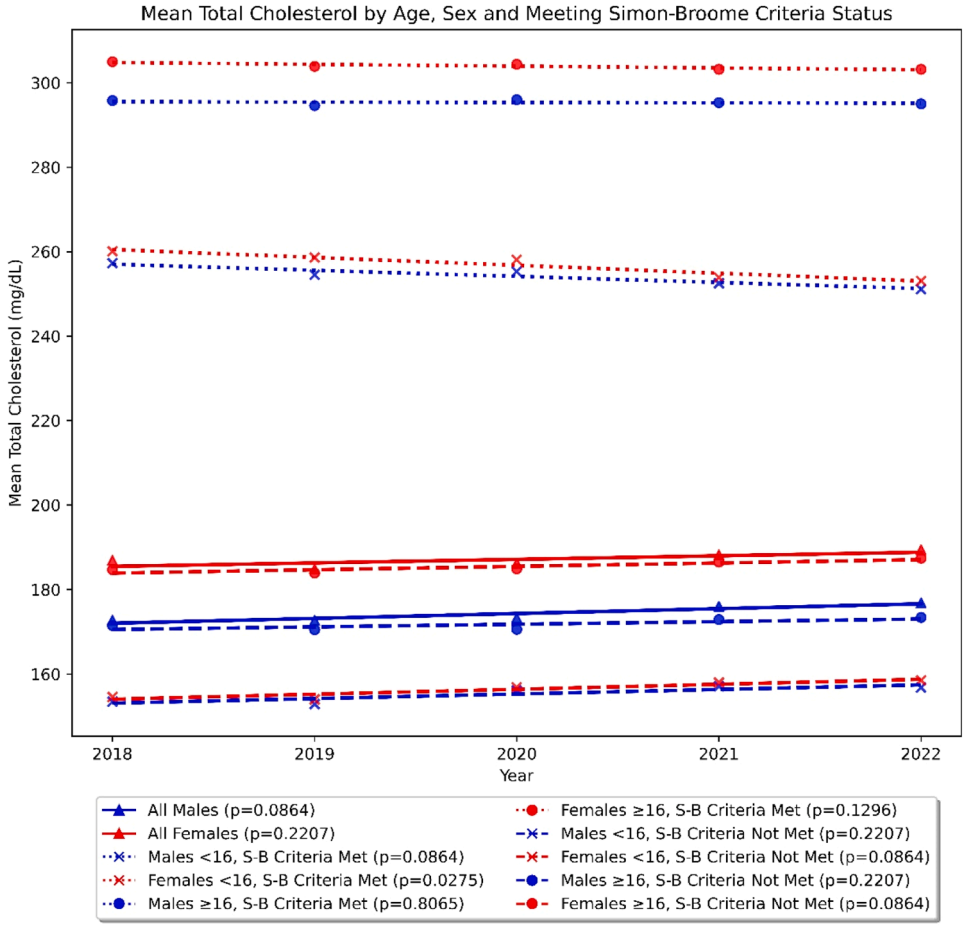


Fig. 2. Year-over-year mean TC trends for patients by sex, age, and whether the patients met Simon Broome thresholds for TC based upon lipid testing. For patients with multiple lipid specimens submitted during a single year, the results from the patient's first specimen were used. For patients with samples submitted annually, each sample was analyzed for the respective year.

FH-associated gene, and 5 homozygotes. The observed gene-specific distribution of P/LP variants was generally consistent with previous findings, showing variants in *LDLR* as most common (seen in ~84 % of samples with an FH variant), followed by variants in *APOB* (~15 %), and variants in *LDLRAP1* and *PCSK9* (~1 % combined).

A subset of 1691 patients had both FH genetic testing and lipid testing at Labcorp® during the study (Table 2); 200 of these patients were found to have at least one P/LP variant in an FH-associated gene; 10 were <16 years of age and 190 were ≥16 years of age. In the <16 years cohort, the mean TC of patients with a P/LP FH variant was 307 ± 108 mg/dL (95 % CI: 240.06, 373.94 mg/dL) and LDL-c was 239 ± 106 mg/dL (95 % CI: 173.30, 304.70 mg/dL) (6.2 ± 2.7 mmol/L, 95 % CI: 4.53, 7.87 mmol/L); 90 % (9/10) of these patients met Simon Broome lipid criteria. In the ≥16 years cohort, the mean TC of patients with a P/LP FH variant was 265 ± 68 mg/dL (95 % CI: 220.57, 309.43 mg/dL) (6.9 ± 1.8 mmol/L, 95 % CI: 5.72, 8.08 mmol/L) and LDL-c was 186 ± 59 mg/dL (95 % CI: 173.74, 198.26 mg/dL) (4.8 ± 1.5 mmol/L, 95 % CI: 4.49, 5.11 mmol/L); 47 % (89/190) of these patients met Simon Broome lipid criteria. For the <16 years cohort, P/LP variant detection rate was 56.3 % (9/16) in patients classified as "Possible FH" as compared to 5 % (1/20) of those classified as "No lipid evidence of FH". For the adult cohort, the P/LP variant detection rate was 24.3 % (89/366) and 7.8 % (101/1289) in the "Possible FH" and "No lipid evidence of FH" categories, respectively.

4. Discussion

From January 2018 - December 2022, more than 58 million unique patients had lipid testing at Labcorp®. Nearly 2 million of these patients (3.6 %) had samples submitted with an ICD-9 or ICD-10 code indicating a diagnosis of FH, yet only about 5 % ($n = 105{,}902$) of patients with an FH diagnosis code met Simon Broome lipid criteria, as determined by a laboratory-developed algorithm based on TC and/or LDL-c levels. This suggests that patients having lipid testing with a presumed diagnosis of FH often have lipid levels below Simon Broome thresholds, potentially because these patients have prior knowledge of their diagnosis and have already implemented lipid-lowering interventions.

Over the 5-year study period, approximately 1.8 million of the >58 million patients that had lipid testing (3.2 % or 1:31) were classified as possibly having FH, including 2961 patients with LDL-c levels suggestive of HoFH (>400 mg/dL, >10.3 mmol/L). Recent evidence estimates the prevalence of HeFH in the US to be approximately 1:200–250 [12,38,39]. Therefore, patients classified as "Possible FH" by the FH Lipid Profile Algorithm would be good candidates for additional clinical evaluation and genetic testing to distinguish FH from other causes of hyperlipidemia (e.g., diet, lifestyle choices, or secondary causes such as liver disease, hypothyroidism or nephrotic syndrome as mentioned by Sturm et al. [13]. In the present study, for patients identified as having both lipid and genetic testing during the study period, P/LP variants were detected in 56 % of pediatric patients and 23 % of adult patients who were categorized as "Possible FH" by the FH Lipid Profile Algorithm. Lack of P/LP variant detection does not rule out genetic causes.

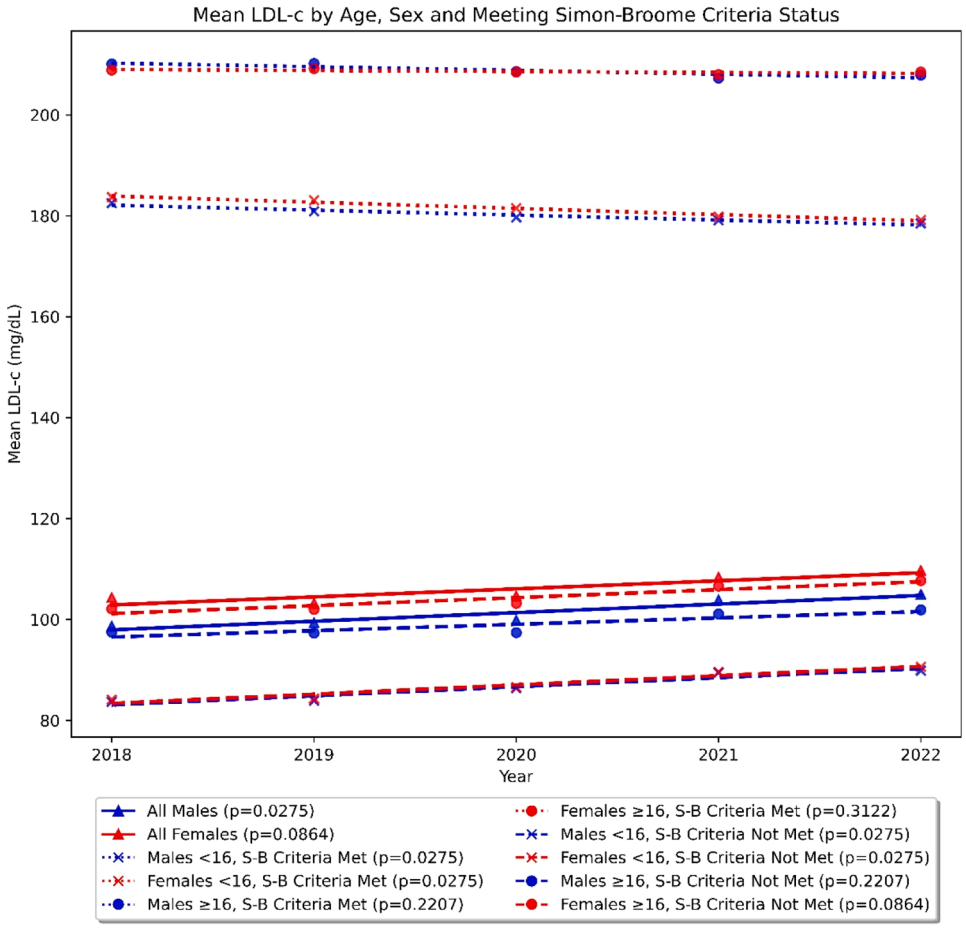


Fig. 3. Year-over-year mean LDL-c trends for patients by sex, age, and whether the patients met Simon Broome thresholds for LDL-c based upon lipid testing. For patients with multiple lipid specimens submitted during a single year, the results from the patient's first specimen were used. For patients with samples submitted annually, each sample was analyzed for the respective year.

Table 4
Samples submitted for FH genetic testing from January 2018–December 2023 (not limited to patients with lipid testing).

Overall cohort	**Number of samples**
Total samples tested	4993
Samples with at least one P/LP* variant identified	418 (8.4 %)
Summary of P/LP results	
Heterozygous variant identified in a single FH-associated gene (HeFH)	411
APOB	63
LDLR	346
LDLRAP1	0
PCSK9	2
Heterozygous variants identified in more than one FH-associated gene	2
APOB+LDLRAP1	2
Homozygous variants identified in an FH-associated gene (HoFH)	5
APOB	1
LDLR	4
LDLRAP1	0
PCSK9	0

* P/LP=Pathogenic/Likely Pathogenic.

Negative genetic testing results could be due to multiple factors, including P/LP variants not detectable due to technical limitations of the assay or miscategorized as an unknown significance based on currently available information, FH caused by a different genetic etiology, either monogenic or polygenic, abnormal lipid profile secondary to other conditions, etc.

Even though FH genetic testing is recommended by several key professional societies, the utilization of this testing appears quite low. In the current study, over 1.8 million patients met Simon Broome lipid criteria from 2018 to 2022, yet fewer than 5000 FH genetic tests were ordered even when the timeframe was extended an extra year (2018–2023) to account for a potential delay in follow-up genetic studies.

Genetic testing for FH is currently able to identify a disease-causing variant in about 60–80 % of individuals with a clinical diagnosis of FH [2]. According to the Genetic Testing Registry, FH genetic testing is available at many commercial and academic labs in the US and in Western Healthcare systems. Furthermore, the collective costs of diagnosing patients with genetic testing and implementing appropriate therapies early in life are wholly offset by the lifetime savings gained across healthcare systems by preventing coronary events and deaths, as well as by gains in quality-adjusted life years [14,40–43]. Many payers consider genetic testing for FH as a medically necessary service subject to beneficiaries meeting clinical criteria, although some payers may impose prior-authorization requirements. (internal data). Identification of a familial mutation allows for efficient and cost-effective cascade testing, which can be particularly helpful in the early identification and treatment of affected children. Additionally, a genetic diagnosis can provide important prognostic and treatment-related information – with certain genes associated with higher or lower lipid levels, likelihood of physical exam findings (e.g., xanthomas), and altered response to

statin-therapy [2]. Genetic testing is particularly important for those patients with lipid levels suggestive of HoFH to ensure initiation of therapy as early as possible and appropriate.

It is important to note that genetic testing may also be indicated for some patients that do not meet Simon Broome lipid criteria. From the current study, 10 % of pediatric patients (1/10) and 53 % of adult patients (101/190) with a P/LP variant in an FH gene did not meet Simon Broome lipid criteria. These patients may have additional FH risk factors, or (particularly in the adult population) may be taking lipid-lowering medications which have normalized their lipid levels. Therefore, lipid results and genetic testing recommendations should be considered in the context of the patient's unique personal and family history.

Year-over-year analysis of lipid panel results showed an increase in the percentage of patients meeting Simon Broome lipid criteria; in 2018, 2.2 % of all patients that had lipid testing met criteria, while in 2022, 2.9 % met those criteria. In patients meeting Simon-Broome lipid criteria, TC remained relatively constant over the 5-year period, and LDL-c levels were even noted to decrease slightly from 2018 through 2022, though mostly not significantly except in the <16 year age group ($p = 0.0275$); this may be evidence of increased awareness of hyperlipidemia, as well as more aggressive treatment of those individuals in a higher risk category. In contrast, for patients not meeting Simon Broome lipid criteria, TC and LDL-c were found to increase over the study period, with LDL-c levels rising by about 7 % from 2018 to 2022; this may be associated with an increase in both pediatric and adult obesity in the US, an increase in lipid panel ordering due to increased awareness of hyperlipidemia in both age groups, due to client organic growth in testing, or due to increased testing after the COVID-19 pandemic.

During the study, females were found to have higher average TC levels than males in both the population of patients meeting Simon Broome lipid criteria and the population not meeting criteria, with more pronounced findings in the adult population. LDL-c levels were relatively similar in females and males who met Simon Broome lipid criteria versus those that did not, regardless of age. These trends are similar to other observations, [29 Tharu] but also differ from a study conducted from 2009- 2011 where men (age 20–59) had higher LDL-c values than women [34]. It has been suggested that elevated levels of LDL-c in women compared to men may be due to resistance to lipid lowering therapies like statins [35]. Women may also receive lower potency drug regimens resulting in the inability to reach LDL-c goals, may face perceived concerns of treatment if of childbearing potential, or experience impacts to drug levels due to increasing visceral fat deposition with increasing age [44,45].

Review of lipid results by geographic region showed that the highest percentage of patients meeting Simon Broome lipid criteria were from the South. This is consistent with the Center for Disease Control and Prevention's data showing a high prevalence of elevated cholesterol in adults across southernmost states, as well as a known greater burden of CVD in this region [46,47]. In such areas, genetic testing has the potential to be particularly helpful in elucidating the etiology of a patient's dyslipidemia and identifying families that could benefit from FH intervention and cascade testing.

This study faces limitations. Patient information available for analysis was limited to the data provided on the laboratory test requisition form; as such, details regarding the patient's clinical presentation, current list of medications (including the use of lipid-lowering medications), family history, race/ethnicity were not available. While more testing was ordered for females when compared to males, this is consistent with studies that females are more likely than males to have seen a physician over a two-year period [48]. There were no means of confirming a diagnosis of FH in a patient; and, when using ICD-9 or ICD-10 codes, it was not possible to determine whether a patient had a presumed or confirmed diagnosis of FH versus a suspicion of FH or a family history of the disease. Additionally, analysis of genetic testing results was limited to tests ordered though Labcorp® during the study timeframe and does not account for individuals tested at other laboratories and/or outside the study timeframe.

5. Conclusion

FH is a common, yet largely underdiagnosed genetic disorder. A laboratory-developed algorithm using Simon Broome lipid criteria, or other FH diagnostic criteria, can help identify patients who may benefit from additional FH evaluation. While critical, testing hyperlipidemic children for FH is grossly underutilized, as is genetic testing for FH. Although there have been several studies advancing strategies to identify patients with probable FH, including screening electronic medical records [12,49] or direct contact with relatives of FH probands [50], to the authors' knowledge, this is the first example of a large-scale strategy to detect possible cases of FH in the general population within a nationwide laboratory network. By applying a laboratory-developed algorithm to the evaluation of lipid panels and adding evidence-based guidance in the form of report comments, the medical laboratory can play a key role in maximizing the identification of potential patients with FH that may benefit from further evaluation and intervention.

Financial interests

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

The authors state that they have not received any funding from any source for this work.

CRediT authorship contribution statement

James K. Fleming: Writing – review & editing, Writing – original draft, Methodology, Data curation, Conceptualization. **Renee M. Sullivan:** Conceptualization, Data curation, Writing – review & editing, Writing – original draft. **David Alfego:** Data curation, Formal analysis, Methodology, Visualization, Writing – review & editing, Writing – original draft. **Natalia T. Leach:** Data curation, Methodology, Visualization, Writing – review & editing, Writing – original draft. **Tamara J. Richman:** Data curation, Visualization, Writing – review & editing. **Jill Rafalko:** Visualization, Writing – review & editing.

Declaration of competing interest

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

Acknowledgements

The authors would like to thank Mimi Barringer, Department of Science and Technology, Labcorp, for her valuable editorial contribution to the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajpc.2025.100930.

References

[1] Harada-Shiba M, Arai H, Ishigaki Y, et al. Guidelines for diagnosis and treatment of Familial Hypercholesterolemia 2017. J Atheroscler Thromb 2018;25(8):751–70. https://doi.org/10.5551/jat.CR003.

[2] Ison H.E., Clarke S.L., Knowles J.W. Familial Hypercholesterolemia. 2014 [Updated 2022 Jul 7]. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. *GeneReviews*®. Available at: https://pubmed.ncbi.nlm.nih.gov/24404629/.

[3] Goldberg AC, Hopkins PN, Toth PP, et al. Familial Hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association expert panel on Familial Hypercholesterolemia. J Clin Lipidol 2011;5:133–40. https://doi.org/10.1016/j.jacl.2011.03.001.

[4] Landstrom AP, Kim JJ, Gelb BD, et al. Genetic testing for heritable cardiovascular diseases in pediatric patients: a scientific statement from the american heart association. Circ Genom Precis Med 2021;14(5). https://doi.org/10.1161/HCG.0000000000000086. e1-e14.

[5] Williams RR, Hunt SC, Schumacher MC, et al. Diagnosing heterozygous Familial Hypercholesterolemia using new practical criteria validated by molecular genetics. Am J Cardiol 1993;72(2):171–6. https://doi.org/10.1016/0002-9149(93)90155-6.

[6] Austin MA, Hutter CM, Zimmern RL, Humphries SE. Genetic causes of monogenic heterozygous Familial Hypercholesterolemia: a HuGE prevalence review. Am J Epidemiol 2004;160(5):421–9. https://doi.org/10.1093/aje/kwh236.

[7] Thorogood M. Risk of fatal coronary heart disease in familial hypercholesterolaemia. scientific steering committee on behalf of the Simon Broome register group. BMJ 1991;303:893–6. https://doi.org/10.1136/bmj.303.6807.893.

[8] McGowan MP, Dehkordi SHH, Moriarty PM, Duell PB. Diagnosis and treatment of heterozygous Familial Hypercholesterolemia. J Am Heart Assoc 2019;8(24):1–16. https://doi.org/10.1161/JAHA.119.013225.

[9] Tada H, Okada H, Nomura A, et al. A reassessment of the Japanese clinical diagnostic criteria of Familial Hypercholesterolemia in a hospital-based cohort using comprehensive genetic analysis. Pract Lab Med. 2020;22:e00180. https://doi.org/10.1016/j.plabm.2020.e00180. /11/01/2020.

[10] Ruel I, Brisson D, Aljenedil S, et al. Simplified Canadian definition for Familial Hypercholesterolemia. Can J Cardiol 2018;34:1210–4. https://doi.org/10.1016/j.cjca.2018.05.01511.

[11] Banda JM, Sarraju A, Abbasi F, et al. Finding missed cases of Familial Hypercholesterolemia in health systems using machine learning. NPJ Digit Med 2019;2:23. https://doi.org/10.1038/s41746-019-0101-5.

[12] Gidding SS, Champagne MA, SDd Ferranti, et al. The agenda for Familial Hypercholesterolemia. Circulation 2015;132(22):2167–92. https://doi.org/10.1161/CIR.0000000000000297.

[13] Sturm AC, Knowles JW, Gidding SS, et al. Clinical genetic testing for Familial Hypercholesterolemia: JACC scientific expert panel. J Am Coll Cardiol 2018;72(6):662–80. https://doi.org/10.1016/j.jacc.2018.05.044.

[14] Nordestgaard BG, Chapman MJ, Humphries SE, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease : consensus statement of the European Atherosclerosis Society. Eur Heart J 2013;34:3478–90. https://doi.org/10.1093/eurheartj/eht273.

[15] Cuchel M, Lee PC, Hudgins LC, et al. Contemporary homozygous Familial Hypercholesterolemia in the United States: insights from the CASCADE FH registry. J Am Heart Assoc 2023;12:e029175. https://doi.org/10.1161/JAHA.122.029175.

[16] Trinder M, Paquette M, Cermakova L, et al. Polygenic contribution to low-density lipoprotein cholesterol levels and cardiovascular risk in monogenic Familial Hypercholesterolemia. Circ Genom Precis Med 2020;13:e002919. https://doi.org/10.1161/CIRCGEN.120.002919.

[17] Trinder M, Cermakova L, Ruel I, et al. Influence of polygenic background on the clinical presentation of Familial Hypercholesterolemia. Arterioscler Thromb Vasc Biol 2024;44. https://doi.org/10.1161/ATVBAHA.123.320287. 00–00.

[18] Beheshti SO, Madsen CM, Varbo A, Nordestgaard BG. Worldwide prevalence of Familial Hypercholesterolemia: meta-analyses of 11 million subjects. J Am Coll Cardiol 2020;75(20):2553–66. https://doi.org/10.1016/j.jacc.2020.03.057.

[19] Benn M, Watts GF, Tybjaerg-Hansen A, Nordestgaard BG. Familial Hypercholesterolemia in the danish general population: prevalence, coronary artery disease, and cholesterol-lowering medication. J Clin Endocrinol Metab 2012;97(11):3956–64. https://doi.org/10.1210/jc.2012-1563.

[20] Cuchel M, Bruckert E, Ginsberg HN, et al. Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the consensus panel on familial hypercholesterolaemia of the European Atherosclerosis Society. Eur Heart J 2014;35(32):2146–57. https://doi.org/10.1093/eurheartj/ehu274.

[21] Hu P, Dharmayat KI, Stevens AT, et al. Prevalence of Familial Hypercholesterolemia among the general population and patients with atherosclerotic cardiovascular disease. Circulation 2020;141:1742–59. https://doi.org/10.1161/CIRCULATIONAHA.119.044795.

[22] Ahmad DZS, Andersen DRL, Andersen DLH, et al. US physician practices for diagnosing Familial Hypercholesterolemia: data from the CASCADE-FH registry. J Clin Lipidol 2016;10(5):1223–9. https://doi.org/10.1016/j.jacl.2016.07.011.

[23] American Heart Association. What is familial hypercholesterolemia? American Heart Association; 2024. Updated 2/19/2024. Accessed 6/3/Reviewed 2/19/2024. Available from: https://www.heart.org/en/health-topics/cholesterol/genetic-conditions/familial-hypercholesterolemia-fh.

[24] Musunuru K, Hershberger RE, Day SM. Genetic testing for inherited cardiovascular diseases: a scientific statement from the American Heart Association. Circ Genom Precis Med 2020;13(4):373–85. https://doi.org/10.1161/HCG.0000000000000067.

[25] Brown EE, Sturm AC, Cuchel M, et al. Genetic testing in dyslipidemia: a scientific statement from the National Lipid Association. J Clin Lipidol 2020;14(4):398–413. https://doi.org/10.1016/j.jacl.2020.04.011.

[26] Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18(6):499–502. PMID: 4337382.

[27] Sampson M, Ling C, Sun Q, et al. A new equation for calculation of low-density lipoprotein cholesterol in patients with normolipidemia and/or hypertriglyceridemia. JAMA Cardiol 2020;5(5):1–9. https://doi.org/10.1001/jamacardio.2020.0013.

[28] United States Census Bureau. Geographic levels. United States Census Bureau; 2024. Accessed 5/15/, Available at: https://www.census.gov/programs-surveys/economic-census/guidance-geographies/levels.html.

[29] HGVS Nomenclature; 2024. Accessed 5/15. Available at http://www.hgvs.org.

[30] Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17(5):406–24. https://doi.org/10.1038/gim.2015.30.

[31] Patel N, Mittal N, Wilkinson MJ, Taub PR. Unique features of dyslipidemia in women across a lifetime and a tailored approach to management. Am J Prev Cardiol 2024;18:100666. https://doi.org/10.1016/j.ajpc.2024.100666.

[32] Mujahid MS, Peterson PM. JAHA go red for women spotlight 2023. J Am Heart Assoc 2023;12:e029832. https://doi.org/10.1161/JAHA.123.029832.

[33] Tharu BP. Tsokos CP A statistical study of serum cholesterol level by gender and race. J Res Health Sci 2017;17(3):e00386.

[34] Swiger KJ, Martin SS, Blaha MJ, et al. Narrowing sex differences in lipoprotein cholesterol subclasses following mid-life: the very large database of lipids (VLDL-10B). J Am Heart Assoc 2014;3(2):1–10. https://doi.org/10.1161/JAHA.114.000851. /04.

[35] Brown CJ, Chang LS, Hosomura N, et al. Assessment of sex disparities in nonacceptance of statin therapy and low-density lipoprotein cholesterol levels among patients at high cardiovascular risk. JAMA Netw Open 2023;6(2):1–12. https://doi.org/10.1001/jamanetworkopen.2023.1047.

[36] von Hafe P. Gender differences in lipid profile and therapy. Rev Port Cardiol 2019;38(8):571–2. https://doi.org/10.1016/j.repc.2019.09.003.

[37] American Heart Association. Understanding homozygous familial hypercholesterolemia. American Heart Association; 2024. Accessed 5/15/, Available at: https://www.heart.org/en/health-topics/cholesterol/genetic-conditions/homozygous-fh.

[38] Faggiano P, Pirillo A, Griffo R, et al. Prevalence and management of Familial Hypercholesterolemia in patients with coronary artery disease: the heredity survey. Int J Cardiol 2018;252:193–8. https://doi.org/10.1016/j.ijcard.2017.10.105.

[39] Watts GF, Gidding S, Wierzbicki AS, et al. Integrated guidance on the care of familial hypercholesterolaemia from the International FH Foundation. Int J Cardiol 2014;171(3):309–25. https://doi.org/10.1016/j.ijcard.2013.11.025.

[40] Jackson CL, Huschka T, Borah B, et al. Cost-effectiveness of cascade genetic testing for Familial Hypercholesterolemia in the United States: a simulation analysis. Am J Prev Cardiol 2021;8:100245. https://doi.org/10.1016/j.ajpc.2021.100245.

[41] Kerr M, Pears R, Miedzybrodzka Z, et al. Cost effectiveness of cascade testing for familial hypercholesterolaemia, based on data from familial hypercholesterolaemia services in the UK. Eur Heart J 2017;38:1832–9. https://doi.org/10.1093/eurheartj/ehx197.

[42] Larazo P, Perez de Isla L, Watts GF, et al. Cost-effectiveness of a cascade screening program for the early detection of Familial Hypercholesterolemia. J Clin Lipidol 2017;11:260–71. https://doi.org/10.1016/j.jacl.2017.01.002.

[43] Rosso A, Pitini E, D'Andrea E, et al. The cost-effectiveness of genetic screening for Familial Hypercholesterolemia: a systematic review. Ann Ig 2017;29:464–80. https://doi.org/10.7416/ai.2017.2178.

[44] von Hafe P. Gender differences in lipid profile and therapy. Rev Port Cardiol 2019;38(8):571–2. https://doi.org/10.1016/j.repc.2019.09.003.

[45] EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC). Global perspective of familial hypercholesterolaemia: a cross-sectional study from the EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC). Lancet 2021;398:1713–25. https://doi.org/10.1016/S0140-6736(21)01122-3.

[46] Centers for Disease Control and Prevention. High cholesterol facts. Accessed 6/2/2024, Avaiable at: https://www.cdc.gov/cholesterol/data-research/facts-stats/?CDC_AAref_Val=https://www.cdc.gov/cholesterol/facts.htm.

[47] Parcha V, Kalra R, Suri SS. 34. Geographic variation in cardiovascular health among american adults. Mayo Clin Proc 2021;96(7):1770–81. https://doi.org/10.1016/j.mayocp.2020.12.034.

[48] Mahalik JR, Backus Dagirmanjian FR. Working men's constructions of visiting the doctor. Am J Mens Health 2018;12(5):1582–92.

[49] Mirzaee S, Choy KW, Doery JCG, et al. The tertiary hospital laboratory; a novel avenue of opportunistic screening of Familial Hypercholesterolemia. Int J Cardiol Heart Vasc 2019;23:1–4. https://doi.org/10.1016/j.ijcha.2019.100354.

[50] Miller AA, Bangash H, Smith CY, et al. A pragmatic clinical trial of cascade testing for Familial Hypercholesterolemia. Genet Med 2022;24(12):2535–43. https://doi.org/10.1016/j.gim.2022.08.026.