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FULL RESEARCH PAPER
Prevention in practice

Global survey of genetic testing methods for familial hypercholesterolaemia: a study and recommendations from the European Atherosclerosis Society Familial Hypercholesterolaemia Studies Collaboration registry

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Aims Familial hypercholesterolaemia (FH), primarily caused by pathogenic *LDLR*, *APOB*, or *PCSK9* variants, results in elevated LDL cholesterol and increased cardiovascular risk. Genetic testing offers the definitive diagnosis, yet global approaches to FH genetic testing remain unstandardized. We investigate current testing practices worldwide and provide relevant recommendations.

Methods and results A survey was distributed to national lead investigators of 68 countries in the Familial Hypercholesterolaemia Studies Collaboration, assessing referral criteria, assay methodologies, target genes, and pathogenicity interpretation methods. National lead investigators from centres in 55/68 countries (81%) responded, spanning Africa (n = 2), Americas

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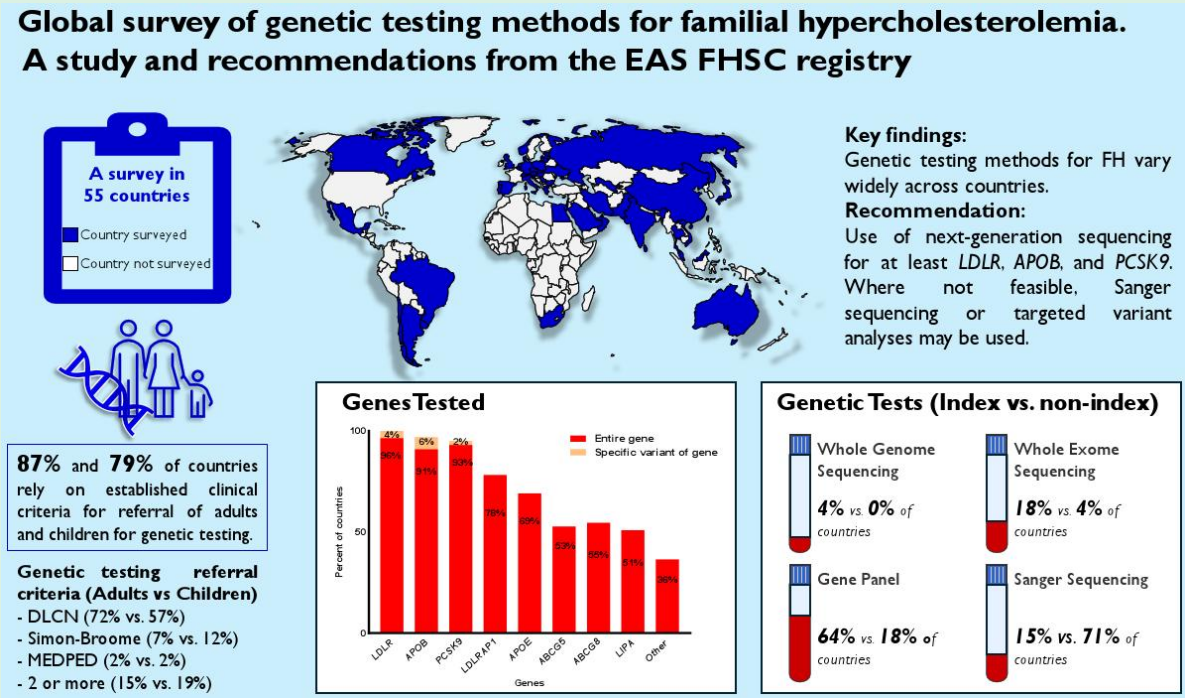
(n = 6), Asia (n = 20), Europe (n = 26), and Oceania (n = 1). Dutch Lipid Clinic Network (DLCN) scores were the most common reason for referral to genetic testing (adults, 72%; children, 57%). Simon–Broome and Make Early Diagnosis to Prevent Early Death (MEDPED) criteria were reported only by centres from high-income countries (adults, 7% and 2%; children, 12% and 2%). Methods for testing in index vs. non-index cases were significantly different (P < 0.001). Next-generation sequencing (NGS) was the predominant assay method for index cases (62%), while Sanger sequencing was favoured for non-index (71%). However, these testing techniques did not differ between centres from high- and non-high-income countries for index cases (P = 0.74) and non-index cases (P = 0.49). Copy-number variants (CNVs) were assessed by 65% of centres, with most integrating CNV analysis into NGS platforms (86%) and others (14%) using multiplex ligation-dependent probe amplification (MLPA) or microarrays. Screening encompassed *LDLR* (100%), *APOB* (97%), *PCSK9* (95%), and other genes. Most centres (96%) incorporated pathogenicity interpretation into their reports, adhering largely to American College of Medical Genetics and Genomics guidelines.

Conclusion Familial hypercholesterolaemia genetic testing practices vary widely across countries surveyed, emphasizing the need for global standardization to enhance accuracy and comparability of FH diagnoses worldwide. We suggest that genetic testing should include the three FH-causing genes and ideally the five associated/phenocopy genes.

Lay summary This was a global survey from centres within 55 countries within the Familial Hypercholesterolaemia Studies Collaboration (FHSC). The study evaluated the current practice of genetic testing for familial hypercholesterolaemia (FH), an inherited condition characterized by high cholesterol levels and increased cardiovascular risk, since a definitive diagnosis is a key determinant of patient-centred care.

- The study found that while most centres screen for the three main FH genes and incorporate interpretation on whether a genetic change is disease causing, notable differences existed in the reasons for referring for a test and laboratory testing techniques among and within centres from high- and non-high-income countries. Among testing techniques, next-generation sequencing was the predominant method for testing index cases, while Sanger sequencing was commonly used for relatives. The study also found that about one-third of centres did not test for other important genetic changes called copy-number variants (CNVs).
- To ensure patients receive accurate diagnoses regardless of where they live, the authors recommend creating a global standard where testing always includes the three primary genes responsible for the condition, ideally alongside five other associated genes.

Graphical Abstract



Keywords Genetic testing • Familial hypercholesterolaemia • Genetics • Pathogenicity interpretation • Global standardization

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Introduction

Familial hypercholesterolaemia (FH) is one of the most common genetic disorders. It is caused by pathogenic variants in the *LDLR*, *APOB*, or *PCSK9* genes and manifests with lifelong elevated LDL cholesterol (LDL-C) and consequently increased risk of premature atherosclerotic cardiovascular disease (ASCVD).[1–3] LDL-C–lowering medications are the cornerstone of treatment of FH and have been shown to substantially reduce the risk of ASCVD and death in this population, if initiated early.[4]

There is a clear value of genetic testing in FH, as it increases the precision of diagnosis, improves risk stratification, enables cascade testing, increases adherence to therapy, and even enables access to new therapies.[5] Early detection is the key to preventing ASCVD and cardiovascular death in individuals with FH, but has proven challenging in most world regions, as it is estimated that 90% of cases worldwide are undetected.[6] Although various clinical criteria have been developed to enable a clinical diagnosis of FH, a definitive diagnosis of heterozygous or homozygous FH (HeFH or HoFH) is only possible via genetic testing.[5] The 2019 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines for the management of dyslipidaemias recommend that FH should be diagnosed using clinical criteria and confirmed, where possible, by genetic testing.[7] Screening for FH is recommended to identify index cases, followed by cascade testing in families, to enable early detection.[5,8] Various countries have implemented, or are in the process of implementing, different screening strategies for FH detection in children and adults. Most screening programmes for FH include genetic testing as part of the diagnostic process.[5]

As FH awareness increases among clinicians through policy advocacy, and as genetic testing becomes more accessible worldwide, there remain important uncertainties in how FH testing is conducted in practice. Key knowledge gaps include information on which clinical criteria prompt healthcare providers to request genetic testing for FH in adults and children, which laboratory methods are used, and how these approaches differ across countries and healthcare settings, particularly between high-income and non-high-income regions. Addressing these questions is crucial for developing standardized guidelines for FH genetic testing.[9] To explore these uncertainties, we conducted a survey of current practices across centres from 55 countries participating in the global Familial Hypercholesterolaemia Studies Collaboration (FHSC) registry, the largest registry of patients with FH to date. The aim is to provide an overview of current practices, highlight areas for improvement, and provide recommendations for best practices for FH genetic testing, to support the standardization of FH detection worldwide.

Methods

The FHSC registry[10] currently consists of more than 80 000 FH participants from 68 countries, with 77 investigators worldwide, including patients with a clinical and/or a genetic diagnosis of HeFH or HoFH. A detailed description of the FH participants included in the registry has been published elsewhere.[11,12] The FHSC project is registered at ClinicalTrials.gov, NCT04272697.

The survey questionnaire is provided in the Supplementary material. The questions focused on the reasons prompting a referral for genetic testing, as well as genetic testing methodologies employed at the centres within each participating country. FHSC national lead investigators (NLIs) from all 68 countries within the EAS FHSC registry that participated in the registry at the time of the present study were invited to complete the FH Genetics Methods Survey. The final deadline to complete the survey was June 2024, 1 year after the survey invitation was sent to NLIs.

Data from the survey were reviewed and cleaned by querying the respective NLIs where needed. Where data were provided from more than one centre within a given country, the inputs were merged into a single response. The analysis was descriptive, providing information on the number (and %) of centres adopting certain methods or approaches to genetic testing. The list of centres from countries included in each United Nations (UN) region (defined according to the United Nations Statistics Division[13]) or income category (defined according to the World Bank[14]) in this study is shown in *Table 1*. An expanded version of the methods is available in the Supplementary material.

Results

Survey completion rate and countries included

A total of 68 countries fulfilled the eligibility criteria for inclusion in the survey and were invited to participate. National lead investigator (NLIs) responses received covered 55 of 68 (81%) countries. Among these, 52 countries contributed a single-centre response (52 responses), and three countries provided multiple-centre responses (nine responses), which were merged by country. This yielded 55 aggregated responses, one per country, hereafter referred to as 'centres'. The countries with responding NLIs are shown in *Table 1*, classified by UN region, UN subregion, and country income status.

Criteria for requesting a genetic test

Adults

Among the 55 centres surveyed, 54 (98%) specified the criteria used for genetic testing referral. Of the latter, 47 (87%) indicated that referral for genetic testing in adults was primarily based upon fulfilling established clinical diagnostic criteria for the probability of having FH, such as Dutch Lipid Clinic Network (DLCN),[15] Make Early Diagnosis to Prevent Early Death (MEDPED),[16] Simon–Broome,[17] specific country criteria (e.g. Canada and Japan), or a combination of these approaches (*Figure 1*; Supplementary material online, *Figure S1*). The DLCN was the most frequently used clinical criterion, utilized in 34 centres (72%). The DLCN threshold prompting referral for genetic testing varied among centres, with eight centres setting it at 6 points, four centres at 5 points, and three centres at 3 points. In some cases, no specific DLCN score was defined. Simon–Broome was used in three centres (6.4%), MEDPED in one centre (2.1%), and a combination of more than one criterion was considered in seven centres (15%).

Twenty (37%) of the respondent centres incorporated individual classical features of FH into their referral process for genetic testing, either as a supplement to the established clinical criteria or as sole considerations. These features included elevated LDL-C, premature CVD, cutaneous FH signs (xanthoma), and

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Table 1 United Nations region, United Nations subregion, and income status of countries with responding FHSC national lead investigators

UN region	UN subregion	Income status	
		High-income	Non-high-income
Africa	Northern Africa		Egypt
	Sub-Saharan Africa		South Africa
Americas	Latin America and the Caribbean	Chile, Uruguay	Argentina, Brazil, Mexico
	Northern America	Canada	
Asia	Central Asia		Uzbekistan
	Eastern Asia	Hong Kong, Japan, Taiwan	China
	South-Eastern Asia	Singapore	Malaysia, Thailand, Vietnam
	Southern Asia		India, Iran, Pakistan, Sri Lanka
	Western Asia	Cyprus, Israel, Kuwait, Oman, Saudi Arabia, United Arab Emirates	Lebanon
Europe	Eastern Europe	Bulgaria, Czechia, Hungary, Poland, Russia, Slovakia	Ukraine
	Northern Europe	Denmark, Estonia, Latvia, Lithuania, Norway, UK	
	Southern Europe	Greece, Italy, Malta, Portugal, Slovenia, Spain	Serbia
	Western Europe	Austria, Belgium, Germany, Luxembourg, the Netherlands, Switzerland	
Oceania	Oceania	Australia	

family history of FH diagnosis or FH features, or a combination of these (see Supplementary material online, *Figure S2A*). Among the 47 centres that primarily used established clinical criteria, 13 (28%) also considered individual classical FH features as supplementary options. In the seven (13%) centres where established clinical criteria were not used, referral for genetic testing was based solely on individual classical FH features (see Supplementary material online, *Figure S2B*). The FH features considered in these seven centres included elevated LDL-C (6/7, 86%), premature CVD (2/7, 29%), cutaneous signs (2/7, 29%), and family history of FH diagnosis or FH features (4/7, 57%) (see Supplementary material online, *Figure S2B*). The specific LDL-C thresholds were not specified by most centres, and where specified (12 centres), they ranged from 155 mg/dL (4.0 mmol/L) to 250 mg/dL (6.5 mmol/L). The most common cut-off was 190 mg/dL (4.9 mmol/L) (eight centres).

Children and adolescents

For children and adolescents, 53 (96%) of the 55 respondent centres indicated a reason for genetic testing referral, while the remaining two centres did not conduct genetic testing in children. Among the respondents, 42 (79%) performed genetic testing in children based on established clinical criteria (*Figure 1*). The most commonly used criteria were DLCN in 24 centres (57%) and Simon–Broome in five centres (12%). The EAS consensus statement[2] was considered in two centres (4.8%), while eight centres (19%) used a combination of two or more criteria.

Referral for genetic testing in children was based, in 21 (40%) of 53 centres, on individual FH features, which either supplemented established clinical criteria or were the only considered options (see Supplementary material online, *Figure S2A*). In 10 (21%) out of the 53 centres where established clinical criteria were not utilized, genetic testing was conducted based solely on either elevated LDL-C in seven centres (64%), premature CVD in two centres (18%), cutaneous signs in two centres (18%), and/or family history of FH diagnosis/features in nine centres (91%) (see Supplementary material online, *Figure S2B*). LDL-C thresholds were not specified for the majority of centres, and when defined (13 centres), they ranged from 130 mg/dL (3.4 mmol/L) to 250 mg/dL (6.5 mmol/L). The commonest cut-off was 190 mg/dL (4.9 mmol/L) (eight centres).

Centres from high-income vs. non-high-income countries

A comparison between high- (n=38) and non-high-income (n=17) countries showed that only centres from high-income countries utilized Simon–Broome and MEDPED criteria for adults or children (see Supplementary material online, *Figures S3* and *S4*). Notably, some centres from high-income countries also employed routine genetic testing for FH due to government implementation programmes.

Methods used for familial hypercholesterolaemia genetic testing

All centres reported using blood for DNA extraction for genetic testing, while 12 centres (22%) reported additionally using saliva.

The methods used for genetic testing in index cases are shown in *Figure 2* and Supplementary material online, *Figure S5*. Most centres (35/55, 64%) used next-generation sequencing (NGS) with a specific gene panel. Other methods included exome sequencing (10/55, 18%), genome sequencing (2/55, 3.6%), Sanger sequencing screening of genes (6/55, 11%), and testing only for common country-specific variants (2/55, 3.6%). Most centres (36/55, 66%) tested for copy-number variants (CNVs),

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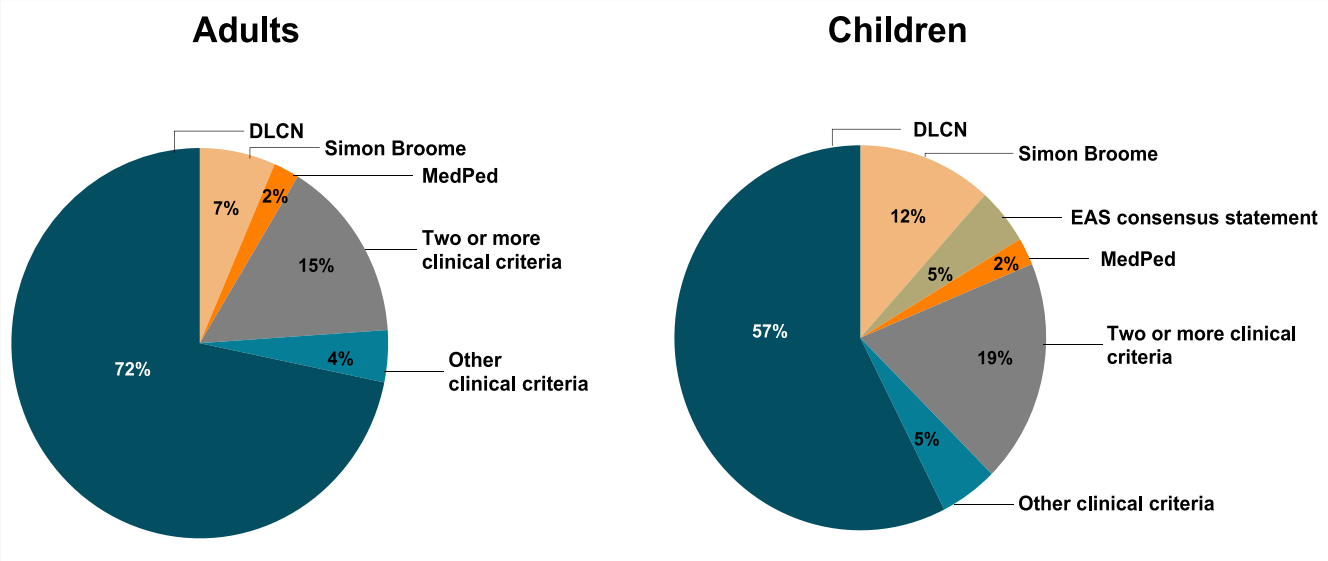

Figure 1 Established clinical criteria used in adults and children among centres that use established clinical criteria. Adults, $N = 47$ centres from 47 countries. Children, $N = 42$ centres from 42 countries. EAS, European Atherosclerosis Society; DLCN, Dutch Lipid Clinical Network; MEDPED, Make Early Diagnosis to Prevent Early Deaths project; other clinical criteria, Japanese Atherosclerosis Society FH criteria, or Canadian FH criteria.

86% (31/36) of these integrated CNV detection into NGS pipelines, and 14% (5/36) employed methods, such as multiplex ligation-dependent probe amplification (MLPA) (4/36) or microarray (1/36).

Regarding genetic testing in non-index cases, the methods used were significantly different from those for index cases ($P < 0.001$). Only 14 of the 51 (27%) centres reported using the same methodology as for index cases: 10 centres use NGS gene panels, two centres use exome sequencing, and two other centres test only for their own country-specific variants by Sanger sequencing (*Figure 2B*). The six centres that screen whole genes by Sanger sequencing in index cases also use Sanger sequencing to test only the variant identified in the family. For 31 centres, the methodology was different for non-index cases, using Sanger sequencing and/or MLPA to test only for the variant identified in the family. In four centres, non-index cases were not tested.

Centres from high-income vs. non-high-income countries

Testing techniques used in centres from high- and non-high-income countries were not significantly different for index cases ($P = 0.74$) or non-index cases ($P = 0.49$). Gene panel sequencing was the method preferred by centres from both high-income (24/38, 63%) and non-high-income (11/17, 65%) countries. In proportion, more centres from non-high-income countries used exome sequencing (24% vs. 16%) or testing of only country-specific variants (6% vs. 3%) to diagnose index cases than from high-income countries. Conversely, only centres from high-income countries used genome sequencing for FH diagnosis. Copy-number variants in index cases were tested in 26/38 (68%) centres from high-income countries and 10/17 (59%) centres from non-high-income countries (*Figure 2B*). Additional details on genetic testing practices by country of testing centre are provided in Supplementary material online, *Table S1*.

Genes screened

Genes screened for by respondent centres are shown in *Figure 3*. All centres (55/55) screened for the *LDLR* gene. A total of 47 centres (85%) screened at least all exons of *LDLR*, *APOB*, and *PCSK9*, regardless of methodology; 32/38 (84%) from high-income countries and 15/17 (88%) from non-high-income countries. Two centres reported screening *LDLR* and *APOB* but not *PCSK9*, while three others screened *LDLR* and *PCSK9* and only specific variants/regions of *APOB*. One centre tested *LDLR* and *PCSK9* but not *APOB*, another centre tested only specific variants in *LDLR* and *APOB*, and another one only tested specific variants in *LDLR* and *PCSK9*. Regarding other FH-associated and FH phenocopy genes, 43 centres screened *LDLRAP1*, 37 screened *APOE* (and one tested only a specific variant), 29 screened *ABCG8*, 28 screened *ABCG5*, and 28 screened *LIPA*. In total, 24/55 (44%) centres screened all exons from the three FH-causing genes, the two FH-associated genes, and the three phenocopy genes; 15/38 (39%) from high-income countries and 9/17 (53%) from non-high-income countries.

A total of 13 centres across 13 countries reported screening for additional genes, although only genes related to the diagnosis of FH were requested. Of these, *APOC2* and *STAP1* were screened for by six centres; *ABCA1*, *APOA5*, and *LPL* by five centres; *CYP27A1* and *GPIHBP1* by four centres; *APOC3*, *LIPC*, *LMF1*, *LPA*, and *SORT1* by three centres; and *APOA1*, *APOA2*, *CREB3L3*, *DHCR7*, *EPHX2*, and *LCAT* by two centres.

Polygenic hypercholesterolaemia

A total of 18 centres across 18 countries (33%) reported testing for polygenic hypercholesterolaemia; 12/38 (32%) from high-income and 6/17 (35%) from non-high-income countries. Of these, eight performed it routinely, while 10 tested only if an FH causal variant was not identified or within the context of

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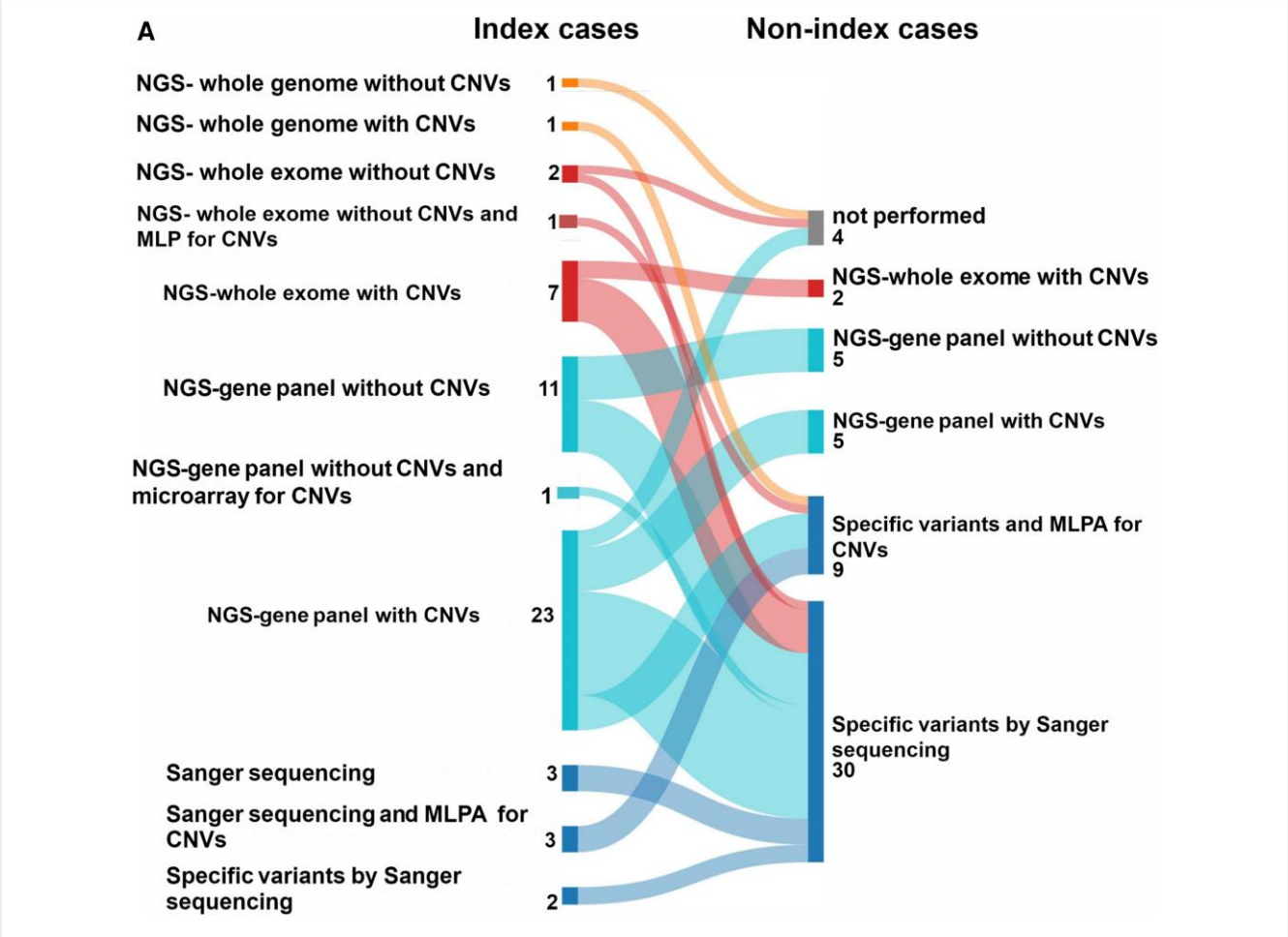

Figure 2 (*A*) Methods of genetic testing among index cases (*N* = 55 centres from 55 countries) and non-index cases (*N* = 51 centres from 51 countries). (*B*) Methods of genetic testing by country income status. The thickness of the vertical lines on the right and left borders of each figure reflect the numbers depicted, which in turn indicate the number of centres using each test. Centres from high-income countries, *N* = 38; centres from non-high-income countries, *N* = 17. NGS, next-generation sequencing; CNVs, copy-number variants; MLPA, multiplex ligation-dependent probe amplification.

research. In six centres, the polygenic score tested was the 6-SNP score described by Futema *et al.*,[18] in seven centres it was the 12-SNP score (Talmud *et al.*[19]) (four of these tested both the 6- and 12-SNP scores), two centres tested the 10-SNP score (Wang *et al.*[20]), one the 28-SNP score (Trinder *et al.*[21]), one the 223-SNP score from the Global Lipids Genetics Consortium,[22] and the remaining four centres did not specify the specific score tested.

Variant pathogenicity interpretation

Pathogenicity reporting for identified variants is standard practice in 53 of 55 respondent centres with only two centres across two countries reporting the variant without providing pathogenicity interpretation. American College of Medical Genetics and Genomics (ACMG) guidelines were the most used criteria (45/53, 85%), either just the general 2015 version[23] (22/53, 42%), modified ACMG guidelines (2/53, 3.8%) (either published[24,25] or not), the Clinical Genome Resource (ClinGen) FH Variant Curation Expert Panel (VCEP) specification for *LDLR* variants[26] (1/53, 1.9%), or a combination of these (21/53, 40%), depending on the gene in question (*Figure 4*). The remaining seven centres stated their method for variant interpretation as consulting databases, such as ClinVar,[27] HGMD,[28] or LOVD,[29–31] or using only segregation or *in silico* analysis.

ClinVar database was reported to be consulted in 26 centres, LOVD in four centres, HGMD in three centres, LSBD-UMD-LDLR[32] in one centre, population frequency databases such as gnomAD and ExAC in four centres, and their own internal databases in two centres. Software tools used in variant interpretation were reported in three centres, namely Varsome, Franklin, and Cardio Classifier. Additionally, 16 centres reported using data from *in silico* analysis, four centres from functional analysis, and three centres from segregation analysis, either alone or in combination.

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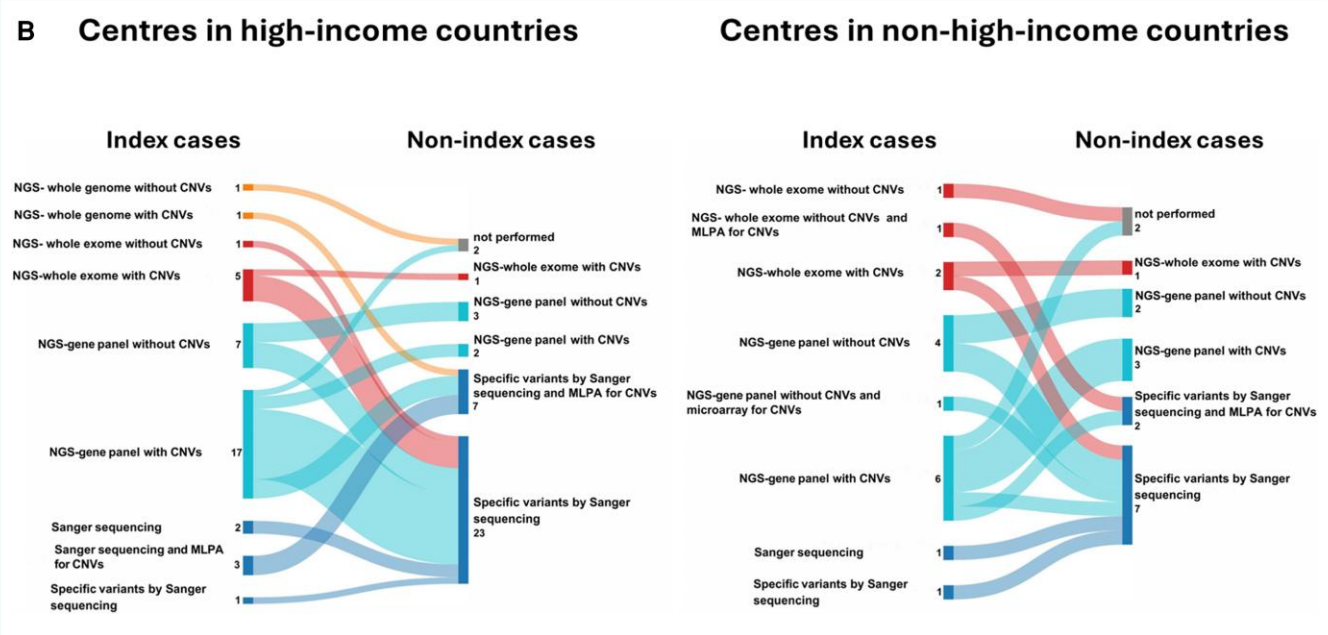

Figure 2 Continued

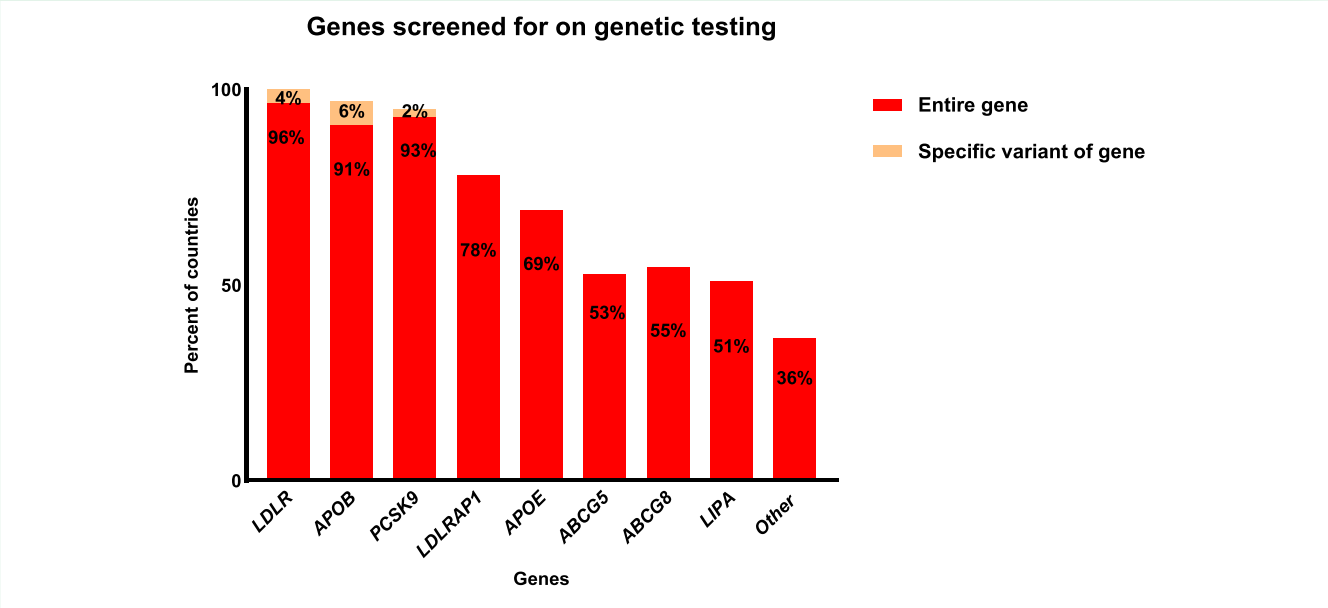

Figure 3 Genes screened for on genetic testing. $N = 55$ centres from 55 countries.

Discussion

The present study provides the most comprehensive description of current practices in FH genetic testing in centres from different countries worldwide using a systematic questionnaire and is the first such attempt globally. Based on the large differences observed in the centres from different countries, best practice recommendations from the FHSC Genetics Working Group for genetic testing of FH are given in a separate section.

Reasons for referral for genetic testing

Our results indicate that centres in most countries surveyed prefer the DLCN criteria over any other criteria for FH diagnosis in both adults and children. This is a surprising finding for children and adolescents, given that the DLCN criteria are not validated in children and lack age-specific LDL-C thresholds, which may limit its sensitivity in children.[33,34] In fact, according to previous reported data from the FHSC, up to 50–75% of

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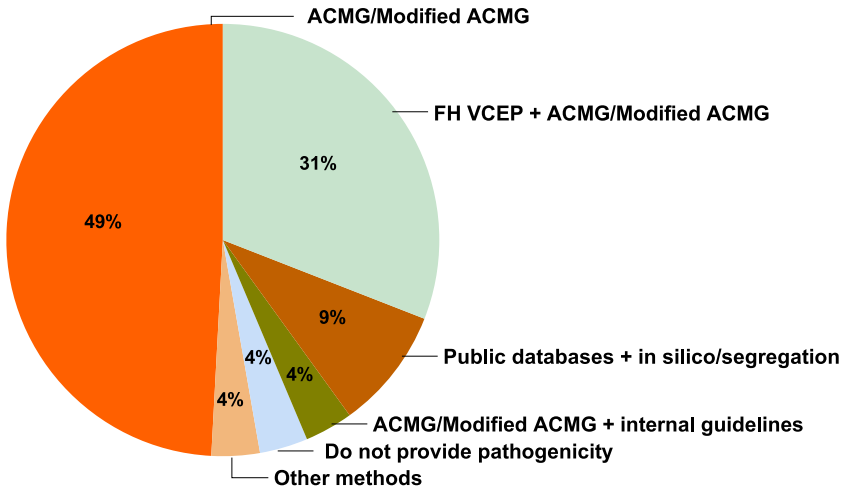

Figure 4 Guidelines for determining pathogenicity. *N* = 55 centres from 55 countries. ACMG, American College of Medical Genetics and Genomics; FH VCEP, Familial Hypercholesterolemia Variant Curation Expert Panel.

children/adolescents with genetic FH could be missed (i.e. clinically not suspected to have FH) if LDL-C thresholds similar to those from DLCN were applied.[12] This preference for DLCN might come from a smaller proportion of paediatric cases in those countries, a larger focus on diagnosing children only by cascade screening, or a lack of awareness of the limitations of DLCN with regard to diagnosing FH in children. Unfortunately, this survey did not differentiate genetic referring for index cases vs. relatives, so cascade screening approaches were not recorded. Simon–Broome criteria and the EAS consensus paper,[2] which specify paediatric LDL-C thresholds, as well as specific paediatric guidelines like the one from the Japanese Atherosclerosis Society,[35] for example, are better suited for diagnosing FH in younger populations.[12,36] Future studies should assess the effectiveness of adapting DLCN thresholds for paediatric populations to improve diagnostic accuracy.[37]

Dutch Lipid Clinic Network is the most used in centres from both high- and non-high-income countries most likely due to it being recommended by the ESC guidelines on cardiovascular disease.[38] Make Early Diagnosis to Prevent Early Death and Simon–Broome are only used in a few centres, mostly in high-income countries. This difference is most likely due to historical guideline adoption, since the data required to apply Simon–Broome and DLCN are largely the same—LDL values, family history, and physical findings—and thus should not reflect differences in resource availability or healthcare infrastructure.

Some of the respondents in the survey reported using more than one of the established clinical criteria, possibly to increase diagnostic inclusivity. Differences in sensitivity and specificity among frameworks, such as DLCN, Simon–Broome, and MEDPED, suggest that no single framework is universally optimal[39] and that combining these criteria may capture cases missed by individual systems. However, this raises questions about the need to tailor diagnostic tools to reflect the genetic, environmental, and demographic characteristics of specific populations. Using more permissive criteria, such as LDL-C thresholds alone, may increase identification of potential FH cases, particularly in cases where family history or more detailed data might be lacking.[40] However, this strategy increases the number of genetic tests necessary, potentially straining resource-limited systems. Alternatively, strict criteria may exclude positive cases with borderline LDL-C concentrations. Striking a balance between sensitivity and specificity is essential, particularly considering specific local prevalence and diagnostic tools.

Familial hypercholesterolaemia genetic testing methodologies

Centres across most countries reported using NGS with a specific gene panel. However, only 47 centres screened the three FH genes, and only 24 included the five genes of FH phenocopies, as recently recommended.[5] We note that centres from several countries reported including the *STAP1* gene in their FH testing panel, even though recent data have demonstrated that variants in this gene do not cause FH.[41,42]

Centres from 12 countries reported using NGS for both index and non-index cases, which is not economically sustainable, as the cost is at least 10 times higher than genotyping in relatives only the variant identified in the index case. In non-index cases, it is only necessary to test the specific variant by either Sanger sequencing of the appropriate exon or MLPA in cases with CNVs. We noted that the use of NGS in non-index cases was more frequently reported by centres from non-high-income than from high-income countries. We hypothesize that this practice might reflect limited access to alternative methodologies rather than a deliberate strategic choice.

Copy-number variants are known to account for ~10% of *LDLR* variants[43]; however, 34% of centres do not incorporate CNV analysis into their NGS pipelines. This omission is remarkable, as the data for CNV detection are often embedded within NGS results and should be accessible using appropriate bioinformatic tools. This is especially important in an FH population genetic screening context. Including CNV detection in existing pipelines would significantly enhance diagnostic yield at minimal additional cost.

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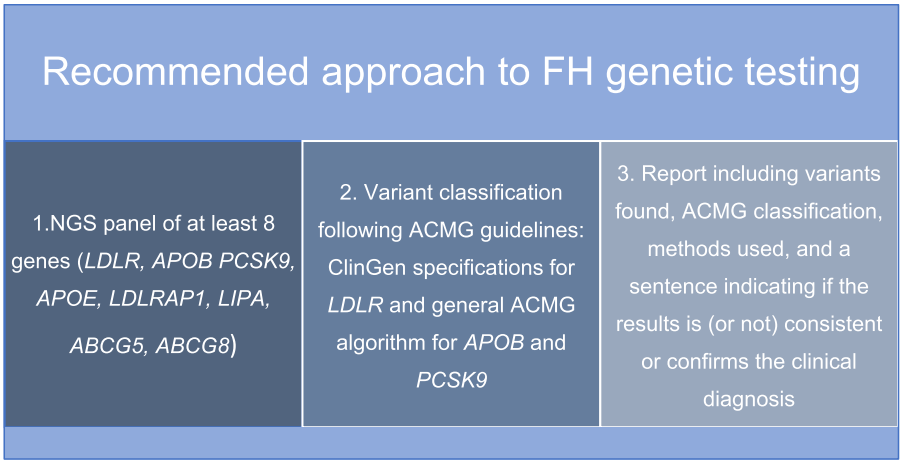

Figure 5 Most important steps in familial hypercholesterolaemia genetic testing.

This heterogeneity in testing practices will inevitably lead to different diagnostic ability, as some techniques are more comprehensive than others. The higher rate of false negatives will directly impact patient care, namely not allowing cascade screening in families and preventing treatment optimization.

Polygenic hypercholesterolaemia

The role of polygenic hypercholesterolaemia in FH diagnosis is increasingly recognized,[44] but its clinical utility remains uncertain. Although still at risk of ASCVD, the polygenic hypercholesterolaemia group has a lower risk than those with monogenic FH[45] and may not require the intensive lipid-lowering therapy recommended for monogenic FH patients. Currently, centres from only 18 of the 55 countries surveyed reported testing for polygenic hypercholesterolaemia, and most test only when a genetic FH diagnosis is not reached or in a research context. It is relevant to highlight that, although this questionnaire did not question who were the patients being tested for polygenic scores, these are not validated for children. Reporting polygenic findings alongside monogenic results might provide context for otherwise unexplained elevated LDL-C concentrations in adults, but consistent reporting guidelines are needed to standardize their interpretation and clinical utility, as can be seen in the high variability of scores used (6-, 12-, 10-, 28-, or 223-SNP scores).

Variant classification

Our results reveal that reporting variant pathogenicity is standard practice in almost all centres included in this study and that ACMG guidelines[23] are widely used. Whenever gene-specific guidelines and expert panel reviewed classifications (3-star) in ClinVar are available, as is the case for *LDLR*,[46] they should be prioritized over general ACMG criteria and 1- or 2-star classifications. Accuracy of variant classification is highly important and depends on access to reliable case-level data, robust databases, *in silico* tools, segregation analysis, functional studies, and population frequency data. Questionnaire responses suggest that these tools may be under-reported, because ACMG guidelines rely heavily on these tools.

Recommendations for familial hypercholesterolaemia genetic testing

Following the results of this study, here are presented recommendations from the FHSC Working Group on Genetics, which aim to improve FH genetic testing worldwide. A summary of these recommendations is shown in *Figure 5*.

Genes to test and methodologies

As recommended by the expert panel on genetic testing for FH,[5] the best genetic test for FH is the use of an NGS panel of eight genes, including the three FH-causing genes (*LDLR*, *APOB*, and *PCSK9*), two associated genes (*APOE* and *LDLRAP1*), and three phenocopy genes (*LIPA*, *ABCG5*, and *ABCG8*), as biallelic (likely) pathogenic variants in these five genes can present a clinical phenotype similar to FH (except p.Leu167del in *APOE*, which in heterozygosity has been associated with FH[47]). In countries where NGS is not possible, FH genetic testing can be performed by Sanger sequencing of each exon of the three FH-causing genes, as in the past. For specific populations with founder effects, the amplification and sequencing of specific fragments where the most common variants are found, or the use of arrays with those variants, can also be used, with the caveat that it must be acknowledged that only those fragments were analysed. Arrays and other selective methods should only be used if they are comprehensive methods with all variants described, so the diagnostic probability is high. Whole exome sequencing (WES) and whole genome sequencing (WGS) with a subsequent analysis of at least the eight genes referred can also be used, but most probably it is not the most cost-effective method in most countries (especially WGS). For family studies (cascade screening), the most cost-effective method is polymerase chain reaction (PCR) amplification and Sanger sequencing of the

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fragment containing the variant found in the family, or MLPA if the variant is a large rearrangement. Using NGS methods for cascade screening can increase the cost 10-fold.

It is crucial to have a method to detect large rearrangements (CNVs), since these constitute ~10% of all variants found in *LDLR*. For NGS, there are software to analyse large rearrangements, and for labs that do not use NGS, MLPA should be performed. The use of arrays for large rearrangements, as comparative genomic hybridization (CGH) arrays, should only be used if those arrays can detect single exon duplications or deletions, because usually those arrays only detect larger rearrangements. In *LDLR*, there are several single exon deletions or duplications that can be missed by this method.

Since the clinical utility of polygenic risk scores in hypercholesterolaemia still remains uncertain, at this time, there is no specific recommendation whether to test or not and how to report it.

Variant interpretation

The most challenging part of the genetic diagnosis is the interpretation of the clinical significance of the variants found. In 2015, the ACMG published a general guideline[23] to classify pathogenicity of variants for genetic testing. The ClinGen FH VCEP has developed specific guidelines for the classification of *LDLR* variants,[26] and a dedicated team of biocurators and experts are classifying all *LDLR* variants in ClinVar.[27] Variants in *APOB* and *PSCK9* have still to be classified with the ACMG general guidelines,[23] including all Sequence Variant Interpretation working group-specific recommendations.[48] However, specific guidelines are in development for these two genes.

The classification of a variant is a complex, but crucial, procedure that requires access to a large set of evidence, such as variant type, localization, variant effect, frequency data in public databases, number of unrelated clinical FH cases with the variant, segregation data in families, functional studies, and *in silico* predictors. It is of great importance that research groups and clinical labs share their findings, including case-level data, in public databases, such as ClinVar.

The best practice should be to perform the ACMG classification (according to specifications for *LDLR* or the general guideline with the general published adaptations for *APOB* and *PCSK9*) for each variant found in clinically diagnosed FH patients by each laboratory. ClinVar 3-star level classifications (which means that they were reviewed by the FH VCEP) can be used directly, but laboratories need to check and report the classification date, particularly for variants of uncertain significance (VUS), since more evidence could have been published in the interim, allowing for re-classification of the variant.

Reporting the results of genetic testing for familial hypercholesterolaemia

Only variants classified as likely pathogenic or pathogenic are considered actionable,[23] and so, many clinical FH patients with a VUS may need to wait until experts are able to gather enough evidence for their variant to change classification and have their diagnosis genetically confirmed (or not).

Following the Association for Clinical Genetic Science (ACGS),[49] when a likely pathogenic variant is found, the report should state that result is *consistent* with the clinical diagnosis, and if a pathogenic variant is found, the report should mention that result *confirms* the clinical diagnosis. The European Society of Human Genetics (ESHG) states that VUS can be reported,[50] especially to medical geneticists. However, since there is the possibility that the referring physician may misinterpret a VUS as pathogenic or may not know how to handle this information, which could lead to a wrong diagnosis or hinder the search for the correct one, a report of a VUS should always be very well elucidated.[51] If co-segregation data can change the variant classification, the request for a family study should be included in the report. For likely benign and benign variants, the report should be given as negative.[50] Although methods for genetic counselling were not covered in this questionnaire, genetic counselling is very important to help patients understand these nuances on the genetic reports.

Lipoprotein(a) measurement

Even though this survey did not collect information about lipoprotein(a) testing, it is important to mention that all patients with hypercholesterolaemia should perform a measurement of lipoprotein(a), as elevated lipoprotein(a) can contribute to a clinical diagnosis of FH in 25–30% of individuals with a clinical diagnosis of FH.[52–54] This is particularly important, as those with both elevated lipoprotein(a) and FH have a higher risk of ASCVD than those only with high lipoprotein(a) or only with a genetic diagnosis of FH.[55]

Strengths and limitations

This study is a comprehensive description of current practices in FH genetic testing in centres from 55 countries worldwide. However, the data from each centre are not necessarily representative of what is practiced across the whole country; rather, it represents the experience of the centres to which the FHSC NLIs are affiliated. These are often centres of excellence for FH management or research centres in their respective countries and thus may reflect best available practice within a given country. Hence, the practices captured within this survey may represent better-resourced settings than the actual practice in other centres within the same country. In addition, collaborations within the FHSC, particularly between centres from high-income and non-high-income countries, have, in some cases, facilitated access to more expensive genotyping methods. Consequently, the information reported for some non-high-income countries may not fully reflect the methods available nationwide. While our findings give a broad, and potentially somewhat optimistic, overview of patterns of genetic testing methods across world regions, they do not represent a comprehensive country-level mapping of these methods. Nevertheless, the information derived should be useful in identifying key gaps in practice and outlining recommendations for optimal genetic testing for FH.

Conclusions

In summary, we report on the practices of FH genetic testing in clinical centres from 55 countries within the FHSC, spanning six continents. A wide variability was observed in the reasons prompting referrals for genetic testing, as well as in the methodologies used for genetic assays and reporting. These findings highlight the influence of country-specific approaches, including variations in healthcare infrastructure, resources, and policies.

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Based on these observations, we provide recommendations aimed at optimizing FH genetic testing worldwide, but we acknowledge the importance of considering the local contexts and specific needs of individual countries.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

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A list of contributors of country data for this study is available as Supplementary material.

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Conflict of interest: Author's disclosures of interest are available as Supplementary material.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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