A Scoping Review of Interventions Increasing Screening and Diagnosis of Familial Hypercholesterolemia

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ABSTRACT

Purpose
Familial Hypercholesterolemia (FH) is one of the most common genetic conditions, with a prevalence of ~1/250 individuals. If left untreated, FH greatly increases risk for cardiovascular disease and premature death. Currently, FH is largely underdiagnosed, and interventions are needed to increase identification. The purpose of this study was to identify effective interventions aimed at increasing FH diagnosis.

Methods
A scoping review of the literature addressing interventions to increase FH detection was conducted. Included studies detailed interventions which increased screening and detection of FH globally. Studies were characterized by intervention type and analyzed for themes using the Consolidated Framework for Implementation Research.

Results
A total of 46 studies were included in the review across 32 countries. All studies were effective in increasing FH detection. Twelve different intervention types were extracted with the most used being cascade and electronic medical record screening-based interventions.

Conclusions
Given the versatility of effective interventions in this review, efforts could explore approaches that maximize identification through a combination of interventions. Our results support one such strategy that uses electronic medical records to screen for index cases and a two-step indirect and direct contact method of index cases' relatives.

INTRODUCTION

Familial Hypercholesterolemia (FH) is a life-threatening autosomal dominant condition characterized by elevated plasma low-density lipoprotein (LDL) cholesterol that occurs at a prevalence of ~1/250 people worldwide. Yet, in this common genetic condition, less than 1% of FH cases are diagnosed in most countries.[1] Interventions to increase FH screening and diagnosis are available but their impact is still limited. Identification of the most promising future directions for interventions to increase FH screening and diagnosis is needed.

FH Diagnosis

Clinical Diagnosis

Internationally accepted clinical diagnostic criteria for FH do not exist, however three sets of criteria are commonly used: Simon-Broome, Dutch Lipid Clinic Network, and Make Early Diagnosis to Prevent Early Death.[2] These diagnostic criteria identify FH using a variety of criteria, including cholesterol concentrations (both total and LDL specific), tendon xanthomas, molecular diagnostics, and family history.[5] FH diagnosis via clinical criteria is determined by the severity and number of criteria met. Simon-Broome allows for diagnosis of definite, probable, and possible FH. Dutch Lipid Clinic Network provides scores which code for definite, probable, possible, or unlikely FH.[3]

Genetic Testing

Most individuals with FH have a variant in the *LDLR*, *APOB*, and/or *PCSK9* genes.[4] Not all individuals clinically diagnosed with FH have FH-associated variants, but rather, are diagnosed by elevated LDL cholesterol levels. Those who have an identified pathogenetic variant are at significantly higher risk for coronary artery disease than those with no variant.[5] Thus, genetic testing is useful not only to confirm the diagnosis but also to provide information about coronary artery disease risk. Despite advancing genomic technology, genetic testing is not universally standard for diagnosing FH. Recently, the FH Foundation convened an expert panel to review the utility of FH genetic testing. They

recommended genetic testing become the standard of care for patients with definite or likely FH, as well as for close relatives who were also likely to be affected.[6]

FH Detection

Cholesterol Screening

The CDC recommends most healthy adults have their cholesterol levels checked every 4-6 years. Individuals who have a family history of heart disease, diabetes or high cholesterol should be checked more frequently. Universal screening of children is recommended by guidelines issued by the National Heart, Lung, and Blood Institute (NHLBI). They recommend that all children between the ages of 9 and 11 receive a cholesterol blood test.[7] In practice, the NHLBI guidelines are not routinely followed with most providers reporting they "never/rarely/sometimes" screened healthy 9- to 11-year-olds.[8]

Cascade Screening

As alternatives to total cholesterol screening like those used in the U.S., some countries utilize genetic cascade screening. Cascade screening relies on the identification of an index case who has been diagnosed with FH. Cascade screening for FH has been proven to be both effective and cost-efficient and has been classified by the CDC as a tier 1 genomic application, with evidence-based recommendations supporting its integration into clinical and public health programs.[9, 10] As of 2010, three countries have established national cascade screening programs — the Netherlands, Spain, and Wales.[11] Addressing barriers to genetic testing for FH, such as recruitment of family members for testing, geographic access to services, and concerns about privacy and discrimination, may help increase the uptake of genetic testing for FH globally.[12, 13]

Importance of Intervention

There is an urgent need for action to increase FH diagnosis and treatment as early medical intervention is critical in reducing risk for inherited heart disease.[1] Examples of interventions include education for physicians on FH risk factors and clinical diagnostic criteria, implementation of genetic screening programs, and establishing clinics dedicated to lipid disorders like FH.[1] By analyzing formerly

implemented interventions, the present scoping review aims to: 1) identify the types of existing interventions that have been used to increase FH detection; 2) describe common characteristics and/or barriers in successful interventions and; 3) outline effective interventions which could be implemented to increase FH screening and diagnosis.

METHODS

Protocol

The protocol and research question for this study were developed using the PICOT methods and are based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement extensions for systematic review protocols and scoping reviews. The scoping review protocol detailed included studies' objectives, definitions of interventions, research questions, eligibility criteria, information sources, search strategy, study records, and data synthesis. The draft protocol was written by HZ and revised following discussion with the research team and librarian staff. The final version of the protocol was pre-registered on the Open Science Framework and is also available upon request.

Literature Search Strategy and Methodology

The methodology and results presented here are in accordance with the PRISMA and the PRISMA-S extension for reporting search strategies, as seen in Figure 1. A comprehensive literature search was developed by a science librarian (MK) and reviewed by a second librarian. Four article databases were searched: Medline via Ovid (coverage: 1946-2020), Cochrane CENTRAL via Wiley (coverage: 1992-2020), Embase via Ovid (coverage: 1947-2020), and CINAHL via EBSCO (coverage: 1981-2020.) All searches were performed on September 8, 2020 and limited to English language results. Full search strategies for each database are shown in Appendix A. Search results were compiled in EndNote X9.3.3 software for deduplication and then screened using Rayyan QCRI[14].

Inclusion Eligibility and Study Selection

Included articles met the following criteria: 1) detailed a study attempting to increase FH identification; 2) utilized an intervention beyond the standard of care; and 3) were published in English.

AP and EW independently screened all potential articles using Rayyan QCRI. An initial 100 articles were reviewed by AP and audited by EW to clarify the inclusion criteria, with a second round of agreement after 500 articles. Following consensus on the second round of review, the remaining articles' titles and abstracts were reviewed and audited. Subsequently, a full-text review of each article was performed using the same process by AP and EW. Seven inconsistencies between AP and EW were resolved by consulting with HZ with final resolution for all with consensus agreement between the three authors. Quality assessments were not performed due to the scoping nature of the review. Included studies were assigned a number 1 through 46, as seen in Supplemental Table 1, and will be referred to as such henceforth.

Data Collection

Data on study characteristics (year, location of study, sample size), aims, and characteristics of the FH interventions were recorded from each study. Characteristics of FH interventions included: the method for identifying people with FH, the main measure of the study, the use of genetic testing, cholesterol levels tested, the classifications of FH used, whether the study identified new cases or increased the diagnostic rate, and the main outcome. Data abstraction was piloted on 10 articles reviewed by AP and EW and modified based on feedback from the team. Once full agreement was reached on the piloted articles, full data abstraction was conducted with each study and audited independently by both AP and EW for ultimate agreement.

Synthesis

The Consolidated Framework for Implementation Research (CFIR), an analysis framework consisting of five domains and 39 constructs, was chosen to allow identification and categorization of the complex factors which influence interventions. CFIR brings together many frameworks into one consolidated framework to examine interventions and how they function. The CFIR has been used across a wide array of studies, including assessments of barriers and facilitators to universal Lynch Syndrome screening and genetic testing for FH. [15]

In a qualitative thematic analysis of intervention type, each study's intervention was categorized based on its study design methods and implementation context. Categorization was performed by one

researcher using an inductive approach and then verified by another, resulting in 12 intervention categories. Only categories with ≥5 included studies were considered and reported on in this study because categories with less than five studies would not have yielded enough data for analysis. Analysis of excluded categories is available upon request. Themes related to intervention implementation and effectiveness were then coded using the CFIR in a deductive approach.[16] The CFIR construct definitions were discussed and defined for the scoping review content following a pilot review of 10 articles by AP and EW and further refined following reviews of another 10 articles. Each study's intervention was then analyzed and categorized according to the predefined CFIR domain and construct definitions. 25 of the 39 total CFIR constructs were coded. The 14 which were excluded did not apply to the reviewed FH interventions. Of the 25, 16 are included in the results due to the frequency across studies and per intervention category. Constructs were included in the discussion based on frequency (low or high), as well if they were cited by the authors as barriers or facilitators. Included studies were coded and audited independently by AP and EW and discrepancies were resolved to reach full agreement.

RESULTS

Study Characteristics

The electronic database searches resulted in 9,291 articles, and this scoping review yielded 46 studies of interventions across 32 countries. Slightly over half of the studies were based out of Europe (26/46) and focused on implementation in a local or community setting. Only one study (43) reported efforts to increase identification of people with FH across multiple countries in a coordinated project. Most studies were published between 2015-2020 (30/46). Supplemental Table 1 summarizes the search strategy and outcomes. The primary outcomes across the papers were 1) the intervention's ability to identify new cases of FH, and 2) the intervention's ability to increase the diagnostic rate of FH. A direct comparison of screening rates was attempted but not possible given inconsistent reporting of outcomes such as age of screening, screening criteria, absolute versus relative screening rates, and others.

Identification and Measurement of FH

The majority of individuals with FH were identified using clinical diagnostic criteria and genetic testing. 17 of the interventions utilized existing clinical criteria or modified clinical criteria as the primary method of FH identification. Genetic testing was the primary method of FH identification in 13 studies (3, 8, 9, 20, 32, 33, 35, 36, 37, 40, 41, 46). Some studies screened for population- specific variants associated with FH (8, 40), but the majority screened for *LDLR*, *APOB*, and/or *PCSK9* variants (3, 9, 19, 32, 33, 35, 36, 37, 41, 46). Nine studies employed a combination of clinical criteria and genetic testing to identify FH in participants (6, 7, 11, 13, 15, 23, 24, 30, 45). Other identification methods included cholesterol screening (17, 29, 39), Apolipoprotein B levels (1, 38), and the use of tools uniquely designed for the intervention (14, 25, 31). Study populations varied in their inclusion of children. 24 of the 46 studies only included adults, 17 included both children and adults, and five focused on screening efforts for children. Studies which employed child-parent or parent-child screening identified FH by genetic testing and LDL measurements (7, 33).

Intervention Categories

Studies are outlined below by the type of intervention implemented to summarize common methods used across interventions and to highlight CFIR. Results were summarized by constructs within the five CFIR domains (Figure 2) and by intervention category (Tables 1 and 2). Ratings of each CFIR construct include present, positive (facilitator), or negative (barrier). Below are the definitions of the constructs discussed (Table 3). Some studies employed multiple strategies in their intervention and are included in Supplemental Table 1 based upon the primary intervention method.

Implementation Constructs Across All Interventions

Implementation constructs related to all five domains were consistently found across all 46 studies (Figure 2). Almost every study (45/46) incorporated the construct of *Reflecting & Evaluating*. The majority (>27/46) also discussed the following constructs: *Innovation Participants*, *Structural Characteristics*, *Needs and Resources of Those Served by the Organization*, *Relative Advantage*, and

Trialability. In contrast, *Relative Priority*, *Readiness for Implementation*, *Networks and Communication*, *External Change Agents*, and *Executing* were rarely discussed (<8/46).

Cascade Screening and Child-Parent or Parent-Child Screening

Cascade screening was in the top two most prevalent intervention methods. In some studies, index cases were already identified (20, 36, 37) while others utilized electronic screening (35) or screening through clinics (3, 5, 6, 16, 19) and community organizations (3) to identify index cases. Eight of the 10 studies which relied on cascade screening utilized genetic testing to diagnose their index cases and relatives with FH. The implementation setting varied from single day screening events (9) to large-scale programs which operated for years (3). One study classified their method as reverse cascade screening, in which children were the index cases and, subsequently, first-degree adult relatives were tested (37). Nine (of 12) cascade screening interventions included both adults and children, and thus, provided intervention recommendations for both populations.

Child-parent and parent-child screening are specialized types of cascade screening. Both studies (7, 33) which implemented one of these methods utilized genetic testing for both parents and children; the child-parent screening program used cholesterol levels in addition to genetic testing for FH diagnosis (7). The settings of each intervention differed: one initiated child-parent screening in a primary care setting at a child's routine immunization visit (7), while the other began parent-child screening after identification by a lipid disorder clinic (33). Both methods were found to diagnose new cases of FH (33) or improve the diagnostic rate (7).

The *Innovation Participants* construct was discussed in all interventions based on a form of cascade screening (Figure 2), mostly regarding the processes of selecting index cases and recruiting family members. The recruitment of family members varied by study: some relatives were contacted directly by medical professionals associated with the family, while others received a note or letter from the index case explaining the utility of screening relatives for FH. Of the total number of studies which discussed the *Engaging* construct (10), half were based on a form of cascade screening (Figure 2). All statements related to *Engaging* found in five of the 12 cascade screening studies centered around efforts

to secure and increase index cases' relatives' uptake of screening. These efforts included establishing methods of direct and indirect contact. Many studies cited the cost-effectiveness of cascade-screening as a benefit and the process of contacting and screening family members as a challenge.

Electronic Screening

Electronic screening varied by method and implementation setting. Some interventions created algorithms which used clinical criteria to screen existing databases or patients' electronic health records and diagnose FH (2, 12, 26, 27, 28, 34, 42) or used electronic clinical codes (25). Four (of 12) electronic screening interventions included both children and adults. Databases varied from broad general practice databases (31) to databases of specific populations like blood donors (26) and patients in a cardiac catheterization laboratory database (29). Others developed their own tools or guidelines to extract patients who met criteria (cholesterol levels, personal history of a cardiac event, age, etc.) as at risk for FH (14, 29, 31). While most interventions were solely operated through electronic screening, one study did follow electronic screening with a nurse-led clinic to identify new index cases more precisely (20). The main barriers noted to this intervention category were patients' electronic health records often were missing necessary information and lack of physician awareness of FH.

The Needs and Resources of Those Served by the Organization was discussed by eight out of 12 electronic screening interventions. Out of the six studies which discussed the *Availability of Resources* related to their intervention, five (2, 14, 27, 29, 34) cited a lack of resources of information or tools necessary to screen electronically, which limited the potential of the electronic screening method (Table 2). The most common lacking resource was the availability of clinical criteria or family history related to FH diagnosis logged in electronic health records and databases.

Molecular Diagnosis

Five studies implemented interventions which used genetic screening for FH. One study utilized clinical criteria in addition to screening for FH-associated variants and found that incorporating genetic testing identified 11 to 14 additional patients with FH, depending on the criteria used (30). Four studies assessed a unique genetic screening protocol to identify population- specific variants (8) or variants in

families with FH that had gone undetected (23, 32, 41). All studies demonstrated that their screening protocols successfully identified new patients with FH (32, 41) or increased the diagnostic rate of variants (8, 23, 30).

The *Relative Advantage* of using genetic testing to identify FH, compared to using clinical criteria, was discussed in all five studies (Table 1). Particularly, genetic testing's high specificity and selectivity were emphasized. Four out of five studies discussed the *Trialability* construct. *Trialability* was noted as important given that genetic testing was not commonly used or had not been evaluated in the population or implementation setting. Of the three studies which discussed the *Adaptability* construct with respect to the method of genetic testing, one noted that the broader generalizability of their positive results may be limited (30). The other two studies discussed the positive potential for adaptation of the intervention in a broader context, as seen in Table 1.

National Registries and Universal Screening Programs

Countries have demonstrated their commitment to increasing FH identification and treatment through the establishment of FH-specific registries and universal screening programs. Registries have the additional goal of increasing physician and public awareness of FH. Of the three national registries included, only one utilized genetic testing (24), while the other two used clinical criteria (15, 44). All three successfully identified and registered new index cases (15, 24, 44). Two studies reported on Slovenia's universal cholesterol screening of pre-school children. All children were screened by trained school physicians and those with positive screening based on family history and cholesterol levels were referred for genetic testing. FH was confirmed in about half of the children referred (45, 46).

The *Needs and Resources of Those Served by the Organization* construct was discussed in all five studies (Table 2). Statements related to the construct centered around the need for a national effort to increase identification of people with FH in their respective countries of implementation. The *Knowledge and Beliefs about the Innovation* construct was discussed in four of the five studies. Participants' knowledge and beliefs related to FH diagnosis, treatment, and the national programs themselves were cited as a challenge (Table 2). The studies reported a variety of barriers to implementation, including

reported participant concerns related to information privacy in registries (15), a refusal to start lipid-lowering therapy due to lack of knowledge about the effects (24), and a lack of awareness of FH and its risks (44, 46). The *External Policy and Incentives* construct was present in three of the 5 studies (Table 2). Two studies reported policies and guidelines related to the formation of registries (15) and required national cholesterol screening in children (45). Post implementation, one study also contributed to the formation of legislative acts that established the importance of diagnosis of FH in Vietnam (24).

DISCUSSION

It is universally recognized that FH is underdiagnosed, but a broad review of efforts beyond the standard of care to increase FH screening and diagnosis remained absent. The purpose of this scoping review was to assess ways in which interventions have increased the detection of FH and to identify potential themes between interventions. Overall, interventions across 46 studies appear to successfully increase FH detection and lead to creative ways to address this public health concern.

Common Intervention Types

Cascade screening and electronic screening were the most commonly utilized methods. The variety of implementation settings for cascade screening interventions in this review highlights its versatility, in addition to its known cost-effectiveness. For example, some interventions initiated cascade screening in specialist centers, while one which successfully increased identification of new FH cases initiated child-parent cascade screening at routine child immunization visits. Regardless of the setting, the primary way index cases were identified by studies in this review was through genetic testing. Genetic testing's use in cascade screening is likely to increase in prevalence due to decreasing genetic testing costs and the lack of ambiguity in results as compared to clinical diagnoses.[9] However, genetic cascade screening is limited given its reliance on continued identification of unrelated index cases.[17]

A common barrier to cascade screening and genetic testing for FH is the process of contacting and recruiting relatives of diagnosed index cases.[4, 18] Five of 12 studies discussed the *Engaging* construct related to the different modes of communication with relatives, including direct and indirect contact, informational aids, and providing resources to index cases. Future interventions may apply this finding by

providing written information about FH and cascade screening index cases that may facilitate conversation with relatives.

Direct contact involves the contacting of relatives by healthcare professionals upon consent of index cases, while for indirect contact, index cases assume responsibility for disseminating information about screening to their family. In a review of 10 FH cascade screening studies, the yield of direct contact, in terms of new cases per index case, was greater than indirect contact.[19] In addition, a survey in collaboration with the Familial Hypercholesterolemia Foundation found 58% of U.S. index cases (11/19) and all international index cases (8/8) indicated willingness to provide healthcare professionals with the contact information of their relatives needed for direct contact.[20]

Direct contact is also effective when provided by nontraditional sources. The process of engaging family members for screening was the focus of a recent study in the U.S., which applied the Dutch model of cascade screening. In this study, when the FH Foundation contacted family members directly, rather than traditional healthcare providers, 55% of families agreed to participate in screening.[21] Indirect contact has advantages as well. In a different study, index cases preferred indirect contact over hypothetical direct contact and were willing to have conversations with family members about the risk of FH when supplied with supportive materials.[22]

The studies in this review which focused on the barrier of communication with families proved successful. All studies which discussed the *Engaging* construct diagnosed new index cases, as well as positively screened and diagnosed relatives. In response to the findings associated with the *Engaging* construct, future interventions could adopt a two-pronged approach: index cases could be provided with educational materials and letters to facilitate conversations with relatives about FH, followed by direct contact from health care providers. This approach would meet the preferences and needs of index cases to initiate contact while also utilizing healthcare providers to communicate the importance and ease of genetic screening for FH.

Along with cascade screening, novel electronic screening interventions hold great promise. All of the electronic screening studies in this review were published between 2015 and 2020. We expect these

interventions to increase in frequency given their potential for systematic, cost-effective screening.[23] The interventions reviewed in this study were effective in identifying new cases of FH and/or increasing the diagnostic rate of FH. However, insufficient clinical information or family history related to FH within EHRs was emphasized in five of the six studies which discussed the *Availability of Resources* construct. Eight out of the 12 studies reviewed in this category were limited by a reliance upon clinical criteria diagnosis and by the type of information present in databases and electronic health records (EHRs). The studies did not specify why the information was absent. One possible explanation is that physicians, especially primary care-based physicians, are not well-versed in FH and its diagnostic criteria. Thus, increased physician awareness of FH, and its corresponding clinical criteria, may help address this concern, especially in primary care-based settings.

The application of electronic screening varied by setting with some more specialized, such as a blood donor database, and others more widely applicable, such as general practice EHRs. This variety is promising because one type of setting was not superior to another for identifying FH. It will be important to continue implementing electronic screening in many settings to determine an optimal protocol.

Given the findings of this review, we propose a strategy that utilizes cascade and electronic screening methods to increase FH identification. Cascade screening and electronic screening interventions could have a greater impact when combined. Studies in this review demonstrate that it is feasible to integrate both screening methods into the daily routine of providers to systematically identify new cases. An electronic screening tool such as The Canning Tool (31), which screens for FH based on eight diagnostic indicators routinely available in general practice EHRs related to DLCN criteria would identify index cases for follow-up with general practitioners and referral for genetic testing. Given that the *Innovation Participants* construct was discussed in all the cascade screen interventions, we recognize the importance of determining a target screening population. Our results suggest that including both children and adults is feasible and advantageous. As such, the electronic screening should include records from pediatricians and adult care providers to maximize the number of index cases identified. For EMR-based interventions to prove effective, however, greater provider awareness and increased access to data that is

specifically searchable for family history is necessary. After index cases have been identified, genetic testing can be utilized to confirm FH diagnosis. As identified by the *Relative Advantage* construct, genetic testing is preferable to clinical diagnoses due to its specificity and selectivity. To have full effect, however, genetic testing needs to be more commonly used by providers and adapted into primary care settings, as noted by the *Trialability* construct. Cascade screening of index cases' first and second degree relatives can follow a genetic diagnosis. Our findings regarding the *Adaptability* construct suggest that genetic testing can be implemented in a variety of settings and expanded beyond the context of a single population. We recommend a combined direct and indirect method of contact: index cases should be provided educational materials to guide conversations with relatives and providers should contact relatives upon consent by index cases. In workflows which are not conducive to direct contact by providers, outside organizations, such as the FH Foundations, can assist in executing contact with relatives. Large scale efforts to measure longitudinal success of such interventions and compliance of general practitioners with national screening guidelines are necessary.

We anticipate challenges with the implementation of a combined electronic screening and cascade screening approach. The *Networks & Communication* construct was discussed only once in all of the electronic screening interventions; without communication between those involved in the electronic screening and those involved in cascade screening, it will be challenging to transition from positive electronic screening results to the initiation of cascade screening. Further, the *Engaging* construct was either not discussed or was a barrier in electronic screening and cascade screening interventions; engagement of staff is necessary for implementation, especially since a combined approach relies upon communication between engaged staff members. While *Knowledge and Beliefs* was discussed positively in both electronic and cascade screening interventions, most interventions did not discuss whether involved individuals' placed value on the intervention, nor whether they were familiar with relevant intervention tasks. Implementation of a combined electronic and cascade screening approach will require that those involved not only are familiar with the intervention's tasks, but also believe in its ability to increase FH detection. The *External Change Agents* construct was rarely mentioned, but a focus on

identifying and involving external stakeholders could increase providers' knowledge and belief in a combined approach. The aforementioned constructs all contribute to a system's readiness for implementation. The *Readiness for Implementation* construct was discussed as a barrier and facilitator to intervention implementation. The success of integrating our proposed screening strategy into a healthcare system will depend upon the institution's readiness for implementation and preparing institutions for implementation will require attention to each of their unique barriers.

Themes Across Interventions

All 46 of the interventions reviewed were successful in identifying new cases with FH and/or increasing the diagnostic rate of FH in their implementation setting. It would be inaccurate to draw direct comparisons between the number of new cases identified due to the interventions' wide ranges in sample size, duration, and stage. In addition, screening rates cannot be compared because some studies only reported on the number of new individuals identified. However, the wide variety of interventions may also be viewed as a positive indicator of the multiple potential options available for increasing FH identification in myriad settings. In addition, across the variety of interventions, many CFIR constructs were discussed, which may serve as a proxy for the quality of interventions (e.g. these are complex and/or multi-level interventions).

As communities and countries look to implement interventions to increase FH identification, the *Needs and Resources of Those Served by the Organization* construct must be considered. This construct was discussed in 30 of the 46 studies and led to interventions tailored to meet the needs of its setting and to address the local causes of underdiagnosis. For example, given that the spectrum of disease is more diverse in multicultural populations, countries with diverse ethnic and cultural populations may want to consider a broader approach to genetic screening for FH. An example of this would be in Brazil, where very little was known about the molecular basis of FH in their patients prior to implementing a cascade screening program (20).

The increase of national FH registries and screening programs also reflects that many countries are considering the needs of their respective populations. This review detailed five novel national

registries and screening programs and one international screening project, indicating that countries are starting to make strides in their awareness of FH and its identification. However, for this category of interventions, participants' *Knowledge and Beliefs* related to FH diagnosis, treatment, and the security of national programs were identified as a barrier to success. Three of the five national studies discussed the *External Policy* construct in the context of relying on existing policy and guidelines to implement FH registries and national cholesterol screening. Policy does impact FH identification programs, highlighting the importance of developing stronger international guidelines and recommendations related to FH and cholesterol screening than currently exist. Conversely, existing programs have the potential to impact policy, as seen in the case of the Vietnam FH Registry, which contributed to the formation of legislative acts which established the social and medical importance of FH and its management in Vietnam (24).

Clearly, current and past FH interventions have the potential to contribute to change in their implementation setting. A piece of this potential is increasing what is known about FH in a specific population. For many of the interventions reviewed, it was evident that their secondary goal was to gather information about the prevalence of FH in their community. While a positive goal, it also highlights the context of unawareness and lack of priority given to FH identification. In fact, even within the reviewed studies, the *Relative Priority* construct was rarely discussed (7/46). *Relative priority* was cited as a significant barrier to universal cholesterol screening in interviews with pediatric primary care providers.[24] The reviewed interventions have potential to provide more information about the state of FH and the necessity of increasing the relative priority of screening and diagnosing FH.

Limitations

Given the focus of a scoping review on gathering a more holistic rather than narrow understanding of interventions, a meta-analysis was not possible. None of the interventions reviewed were randomized control trials, so it was not possible to draw significant comparisons on the interventions' levels of impact versus the primary standard of care. Many countries were covered in this review, but a cross-country comparison was not performed given the small sample of interventions per country. Lastly, in keeping with the goal to generate holistic understanding, we used an implementation

science framework lens to analyze these interventions, therefore a detailed comparative effectiveness of interventions cannot be inferred from this overview.

Future Directions

This review has detailed 46 interventions which successfully increased FH diagnosis and can serve as models for future tools and programs to increase FH awareness, screening, and diagnosis. It has also allowed for the identification of commonly implemented types of interventions and the themes which exist within and across those categories using the CFIR. The scoping review format allowed for a wide breadth of information to be gathered which could be used to identify areas for future research and more narrow systematic reviews. As previously mentioned, outcomes such as screening and diagnostic rate could not be compared across studies, leaving an opportunity for future research which harmonizes and compares these outcomes. Future areas of research may also include more in-depth explorations of interventions by category and potential evaluation of interventions by country or clinic context given the variability in health care systems across the world.

Data Availability

Authors can choose to supply their data and materials individually upon request or deposit their data in a suitable repository.

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Author Contributions

Conceptualization: H.Z. M.K., K.B.; Data curation: M.K., K.B.; Formal analysis: H.Z., E.W., A.P., Funding acquisition: N/A, Investigation: Formal analysis: H.Z., E.W., A.P.; Methodology: H.Z., E.W., A.P. M.K., K.B.; Project administration: H.Z.; Resources: H.Z.; Software: H.Z., E.W., A.P.; Supervision: H.Z.; Validation: H.Z., E.W., A.P.; Visualization: E.W., A.P.; Writing-original draft: H.Z., E.W., A.P. M.K., K.B.; Writing-review & editing: H.Z., E.W., A.P. M.K., K.B.

Conflicts of interest

Disclosure: The authors declare no conflict of interest.

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Table I:

		Domains															
		Intervention Characteristics			Outer Setting		Inner Setting					CoI	Process				
Intervention Category	Paper	Relative Advantage	Adaptability	Trialability	Needs & Resources	External Policy and Incentives	Structural Characteristics	Networks & Communications	Relative Priority	Readiness for Implementation	Available Resources	Knowledge and Beliefs	Engaging	External Change Agents	Innovation Participants	Executing	Reflecting & Evaluating
Molecular Diagnosis	8	--	0	--	--	0	0	0	--	0	0	0	0	0	--	0	--
	23	--	P	--	--	0	--	0	--	0	--	P	0	0	--	0	--
	30	--	N	--	0	--	--	0	0	0	0	0	0	0	--	0	--
	32	--	P	0	--	0	--	0	0	0	0	0	0	0	--	0	--
	41	--	0	--	--	0	0	0	0	0	N	0	0	0	--	0	--
Cascade/ Child-Parent/ Parent-Child	3	--	P	0	0	--	--	0	0	0	0	P	--	0	--	0	--
	5	--	0	--	0	0	--	0	0	0	N	0	0	0	--	0	--
	6	--	0	0	--	--	0	0	--	0	0	0	0	0	--	0	0
	7	--	0	--	0	0	--	0	0	0	0	0	0	0	--	0	--
	9	--	0	--	--	0	0	0	0	0	0	0	0	0	--	0	--
	16	--	0	--	0	--	--	0	0	0	0	P	0	0	--	0	--
	19	0	0	--	--	0	--	0	0	0	--	--	--	0	--	0	--
	20	0	0	--	--	--	--	0	0	0	0	0	--	0	--	0	--
	33	0	0	--	--	0	--	0	0	0	0	0	0	0	--	0	--
	35	0	0	--	0	0	--	0	0	0	0	P	--	0	--	0	--
	36	--	0	0	0	--	--	0	0	N	0	0	--	0	--	0	--
	37	--	0	0	--	0	0	0	0	0	0	0	0	0	--	0	--

Table II:

		Domains															
		Intervention Characteristics			Outer Setting		Inner Setting					CoI	Process				
Intervention Category	Paper	Relative Advantage	Adaptability	Trialability	Needs & Resources	External Policy and Incentives	Structural Characteristics	Networks & Communications	Relative Priority	Readiness for Implementation	Available Resources	Knowledge and Beliefs	Engaging	External Change Agents	Innovation Participants	Executing	Reflecting & Evaluating
Electronic Screening	2	--	P	--	--	0	--	0	0	0	N	0	0	0	0	0	--
	12	--	0	0	0	--	--	0	0	0	0	0	0	0	0	0	--
	14	0	P	--	--	--	--	0	0	P	N	0	--	0	--	0	--
	21	0	0	--	--	--	--	--	--	P	0	0	0	0	--	0	--
	25	--	N	0	0	0	0	0	0	N	0	--	0	0	0	0	--
	26	0	0	--	0	0	0	0	0	0	0	0	0	0	--	0	--
	27	0	0	0	--	--	--	0	0	N	N	P	0	0	0	0	--
	28	--	--	--	--	0	--	0	0	0	0	--	0	0	--	0	--
	29	--	--	0	--	0	0	0	--	P	N	0	0	0	0	0	--
	31	0	P	0	--	0	0	0	0	0	P	0	0	0	0	0	--
	34	--	P	--	--	0	--	0	0	0	N	0	0	0	0	0	--
	42	--	0	0	0	--	0	0	0	0	0	0	0	0	--	0	--
National Registry/ National Universal screening	15	--	0	--	--	--	--	0	0	N	N	N	0	0	--	0	--
	24	0	P	--	--	--	0	0	--	0	--	N	0	--	--	0	--
	44	0	0	0	--	0	--	0	0	0	N	N	--	0	--	0	--
	45	0	0	0	--	--	--	0	0	0	0	0	0	0	--	0	--
	46	0	0	0	--	0	0	0	0	0	0	N	0	0	0	0	--

Table III:

	Construct	Definition
Intervention Characteristics	Relative Advantage	Stakeholders' perceptions of the advantage of implementing the intervention versus an alternative strategy to increase screening.
	Adaptability	The ability to test their intervention method on a small, reversible scale.
	Trialability	The ability of the intervention to be applied to varied settings.
Outer setting	Needs and Resources of Those Served by the Organization	The intervention's awareness of and focus on its ability to fill a specific area of underdiagnosis within their implementation community.
	External Policy and Incentives	External strategies to spread the intervention including policy and regulations, external mandates, recommendations, and guidelines.
Inner Setting	Structural Characteristics	The physical and social setting of the intervention.
	Networks and Communication	The nature and quality of communication between members of the organization implementing the intervention.
	Relative Priority	The relative prioritization of the implemented intervention as a method of FH detection within the organization and its chosen population.
	Readiness for Implementation	The organization's readiness to implement their intervention with existing structures.
	Available Resources	The absence or presence of resources vital to implementation of the intervention including space, materials, and time.
Characteristics of Individuals	Knowledge and Beliefs about the Innovation	Individuals' value placed on the intervention and familiarity with relevant tasks
Process	Engaging	Engagement strategies and methods related to participant and staff recruitment.
	External Change Agents	Individuals who aren't directly affiliated with the implementing organization who formally influence or facilitate intervention decisions in a desirable direction.
	Innovation Participants	The process and qualification for identifying and recruiting intervention participants.
	Executing	Carrying out or accomplishing the intervention according to plan.
	Reflecting and Evaluating	Assessments of how implementation occurred, the state of the community post-implementation, and the impact the study had on identification of people with FH.

Figure 1:

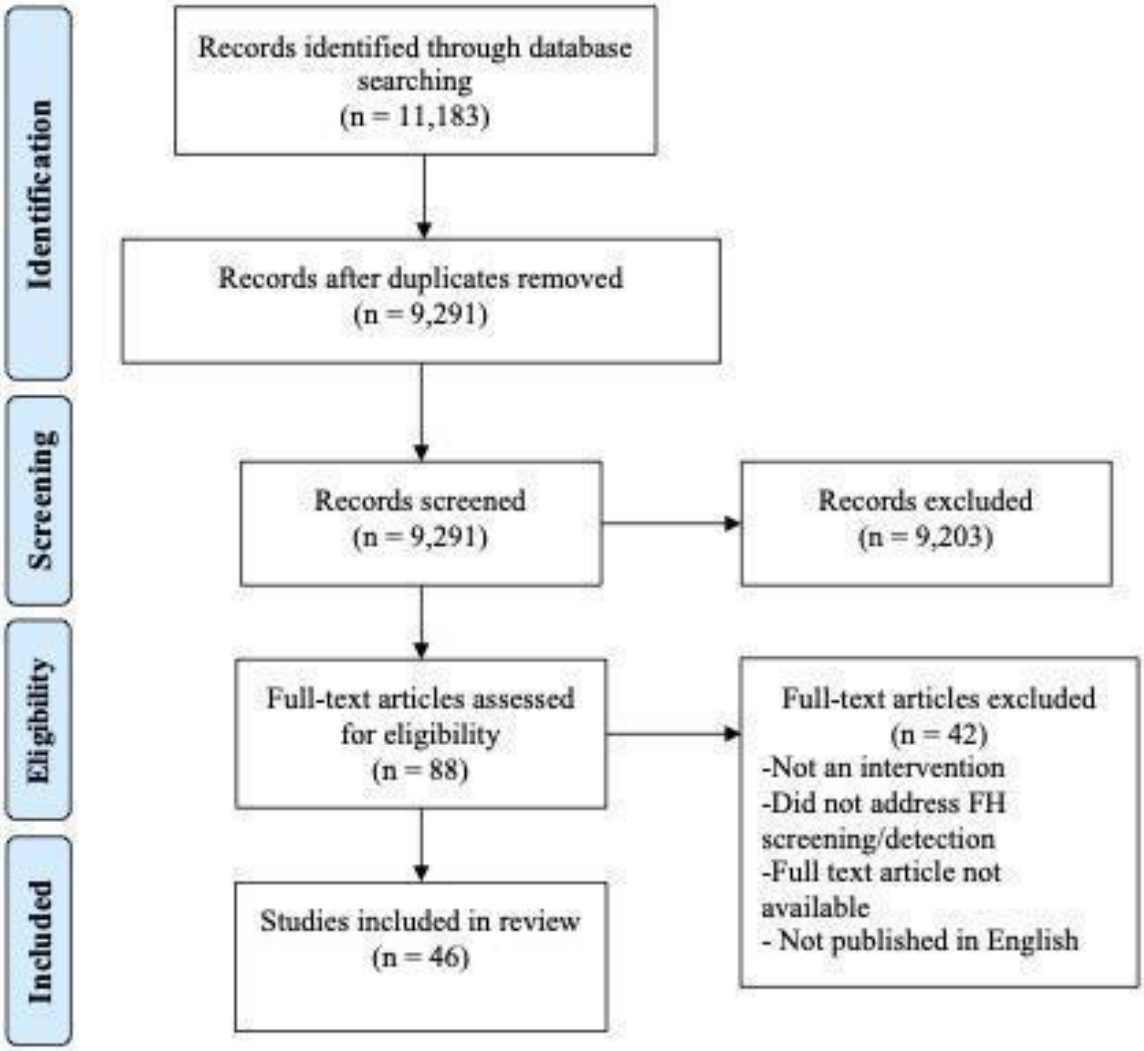
Identification
Screening
Eligibility
Included
Records identified through database searching (n = 11,183)
Records after duplicates removed (n = 9,291)
Records screened (n = 9,291)
Records excluded (n = 9,203)
Full-text articles assessed for eligibility (n = 88)
Full-text articles excluded (n = 42)
-Not an intervention
-Did not address FH screening/detection
-Full text article not available
- Not published in English
Studies included in review (n = 46)

Figure 2:

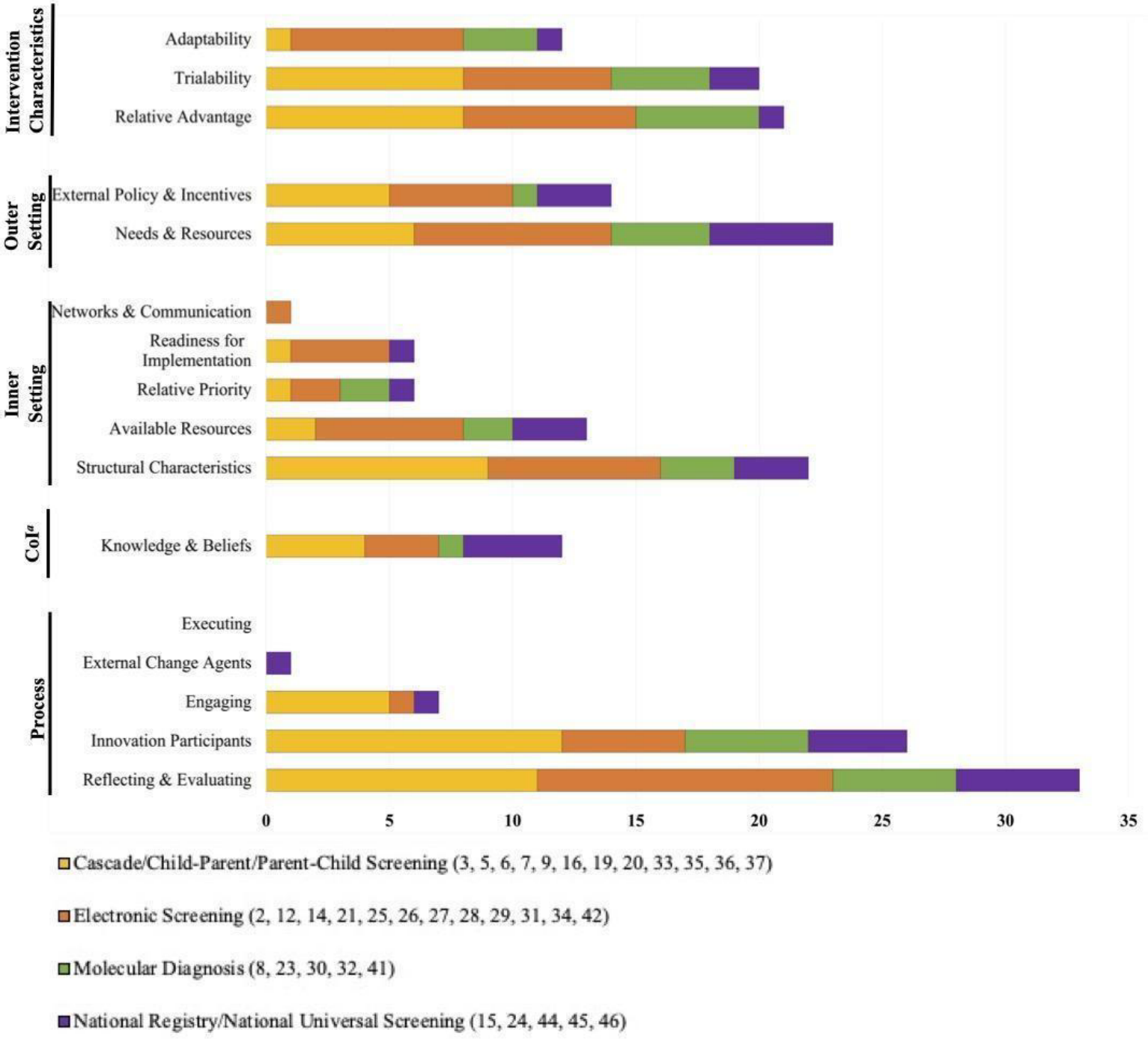
Intervention Characteristics
Adaptability
Trialability
Relative Advantage
Outer Setting
External Policy & Incentives
Needs & Resources
Inner Setting
Networks & Communication
Readiness for Implementation
Relative Priority
Available Resources
Structural Characteristics
CoI[a]
Knowledge & Beliefs
Process
Executing
External Change Agents
Engaging
Innovation Participants
Reflecting & Evaluating
0
5
10
15
20
25
30
35
Cascade/Child-Parent/Parent-Child Screening (3, 5, 6, 7, 9, 16, 19, 20, 33, 35, 36, 37)
Electronic Screening (2, 12, 14, 21, 25, 26, 27, 28, 29, 31, 34, 42)
Molecular Diagnosis (8, 23, 30, 32, 41)
National Registry/National Universal Screening (15, 24, 44, 45, 46)

Figure Legends:

Table I. CFIR constructs summary for each study in the cascade screening and molecular diagnosis intervention categories. Constructs not discussed by studies are annotated with a 0, constructs discussed neutrally are annotated with a light blue --, constructs discussed with a noted positive and negative impact are annotated with a P in light green and an N in light purple respectively.
[a]C of I = Characteristics of Individuals

Table II. CFIR constructs summary for each study in the electronic screening and national registry/national universal screening intervention categories. Constructs not discussed by studies are annotated with a 0, constructs discussed neutrally are annotated with a light blue --, constructs discussed with a noted positive and negative impact are annotated with a P in light green and an N in light purple respectively.
[a]C of I = Characteristics of Individuals

Table III. CFIR constructs' definitions. CFIR constructs discussed in the review are grouped by domain. Each CFIR construct definition is listed as it was adapted for the context of this review.

Figure 1. PRISMA diagram of search and selection process. Articles were identified using the search criteria detailed in Appendix A. Deduplication was performed in EndNote X9.3.3. Of the 88 full- text articles assessed for eligibility, 42 were excluded for not meeting inclusion criteria. 46 studies met inclusion criteria and were included in the final review.

Figure 2. Number of studies with each CFIR construct divided by intervention category. The number of studies which discussed each construct is shown with the five CFIR domains outlined below their respective constructs. The number of studies from each intervention category which discussed that construct are represented by their designated color as seen in the legend.
[a]C of I = Characteristics of Individuals