Implementation science and genetic testing for familial hypercholesterolemia

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Purpose of review
Familial hypercholesterolemia is a treatable genetic disorder of cholesterol metabolism. Genetic testing is the most specific method for diagnosing familial hypercholesterolemia, but it remains underutilized. Implementation science aims to bridge the gap between evidence and practice and, thereby, support improved familial hypercholesterolemia care. This review presents the current evidence on the use of implementation science to improve the use of genetic testing for familial hypercholesterolemia.

Recent findings
Recent research has focused on developing implementation strategies to improve the use of genetic testing, particularly cascade testing of at-risk blood relatives of known familial hypercholesterolemia cases. Stakeholder informed strategies aimed at improving communication between families and detection of familial hypercholesterolemia in primary care have been developed and implemented. Findings demonstrate implementation science methods can help remove barriers and improve the uptake of cascade genetic testing.

Summary
Significant gaps in familial hypercholesterolemia care emphasize the importance of practical and realistic approaches to improve the detection of this preventable cause of premature heart disease, and recent efforts using implementation science have shown some promising results. More implementation science studies are needed that address the considerable gaps in familial hypercholesterolemia care, including the underutilization of genetic testing, so that all individuals receive the best clinical care.

Keywords
cascade screening, cascade testing, cholesterol, evidence translation, lipids

INTRODUCTION

Familial Hypercholesterolemia is an autosomal dominant inherited disorder that causes elevated LDL cholesterol (LDL-c) from birth. Familial hypercholesterolemia is a common condition affecting approximately 1 in 311 people worldwide [1]. Familial hypercholesterolemia is considered a tier 1 genomic application by the Centers for Disease Control and Prevention (CDC), which means it is a preventable cause of cardiovascular disease and death, supported by strong evidence-based guidelines [2]. Despite national and international guidelines [3–6], significant gaps in care remain, and familial hypercholesterolemia continues to be underdiagnosed and undertreated [7]. Gaps in familial hypercholesterolemia care have prompted a growing emphasis on research efforts that utilize implementation science methods to improve the detection and management of familial hypercholesterolemia [4]. Efforts span the familial hypercholesterolemia journey from diagnosis to management and include implementation science methods to address barriers and facilitators, guide implementation phases, develop context specific strategies, and evaluate outcomes [8▪,9▪,10,11▪▪]. This review covers recent research published since

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KEY POINTS

- Genetic testing is the most specific way to diagnose familial hypercholesterolemia and should be a part of routine screening for familial hypercholesterolemia.
- Despite strong evidence-based guidelines, familial hypercholesterolemia remains underdiagnosed and undertreated.
- Implementation science methods should be included in research efforts to reduce the evidence to practice gap in genetic testing for familial hypercholesterolemia.

February 2023 on the use of implementation science to reduce the recognized gap in care in genetic testing for familial hypercholesterolemia.

DETECTION OF FAMILIAL HYPERCHOLESTEROLEMIA

The detection of familial hypercholesterolemia begins with screening of individuals through a review of plasma LDL-c, family history, and possibly genetic testing [12]. Most screening programs begin by identifying individuals with familial hypercholesterolemia using clinical tools such as the Dutch Lipid Clinic Network (DLCN) or Simon Broome criteria with recommendations to confirm the diagnosis through genetic testing [13▪]. Several strategies are used to screen for familial hypercholesterolemia, including opportunistic, systematic, universal, and selective approaches [13▪]. For example, during routine medical examinations healthcare providers can opportunistically screen patients based on an LDL-c concentration of at least 190 mg/dl (>4.9 mmol/l), while systematic approaches include the step-by-step process of testing at-risk relatives for a known pathogenic variant [13▪], an approach with high sensitivity and specificity [14]. Universal screening focuses on specific populations such as children, which is in line with evidence-based guidelines that recommend detection and treatment for familial hypercholesterolemia begin as early in life as possible [15]. Significant progress in diagnosing familial hypercholesterolemia has been made in several countries where screening programs may include phenotypic and or genetic testing [16,17]. However, Slovenia is the only country with a national universal screening program with over 50% of referred children genetically confirmed to have familial hypercholesterolemia [18]. As such, there is a need for global improvements in the use of genetic testing for familial hypercholesterolemia.

BENEFITS OF GENETIC TESTING FOR FAMILIAL HYPERCHOLESTEROLEMIA

The benefits of genetic testing are well established, as evidenced by its inclusion in evidence-based guidelines for individuals with a high likelihood of familial hypercholesterolemia based on phenotypic assessment [13▪,19]. Genetic testing is the most specific approach for diagnosing familial hypercholesterolemia, which can lead to improved access to therapies, better management, and greater adherence to treatment plans, particularly when testing is carried out in childhood [13▪,20]. Genetic testing in childhood is especially important when clinical signs are not yet present as early initiation of therapy can significantly reduce the risk of developing premature cardiovascular disease [21]. Genetic testing may also have prognostic value as research has shown individuals with elevated LDL-c (≥190 mg/l) and certain gene changes are at greater risk for coronary artery disease compared with those with elevated LDL-c and no mutation [22]. Finally, genetic testing facilitates cascade screening (testing of at-risk relatives of an individual with genetically confirmed familial hypercholesterolemia [23]). The benefits of genetic testing have led to its recognition as an essential component of successful familial hypercholesterolemia screening programs [24], with expert recommendations for integrating genetic testing as a standard element of care [23].

GENETIC TESTING IS UNDERUTILIZED DESPITE THE BENEFITS: A GAP IN FAMILIAL HYPERCHOLESTEROLEMIA CARE

Several studies highlight the significant gaps in familial hypercholesterolemia care, including the underutilization of genetic testing [7,25,26]. Genetic testing for familial hypercholesterolemia may be underutilized owing to several factors, including limited awareness and knowledge of familial hypercholesterolemia, restricted or limited access to testing services, concerns about discrimination and privacy, and fears around cost and insurance coverage [27–29]. However, genetic testing is reimbursed in some healthcare systems and some jurisdictions prevent insurance discrimination [30]. Some providers may underestimate the clinical benefit of genetic testing and instead rely on phenotypic assessments [31]. There is limited acceptance in the United States for familial hypercholesterolemia cascade testing with less than 10% of children genetically confirmed [32,33], while in Canada, despite international recommendations, genetic testing remains underutilized with testing services unavailable in some

provinces [28]. The low use of genetic testing, despite its clear benefits in improving familial hypercholesterolemia care, emphasizes the need to address this gap in care.

WHY IS IMPLEMENTATION SCIENCE IMPORTANT TO IMPROVE GENETIC TESTING FOR FAMILIAL HYPERCHOLESTEROLEMIA?

Implementation science is the scientific study of methods to support the systematic uptake of evidence-based guidelines into routine practice [34]. Implementation science theories, models and frameworks have been used to address the significant gaps in familial hypercholesterolemia care by identifying barriers and facilitators, developing solutions using context-specific strategies, and monitoring and evaluating progress [35▪,36▪▪]. There are increasing calls to incorporate implementation science frameworks into research designs across all stages to address evidence to practice gaps in complex healthcare systems [37–39]. This has been described in recent publications that provide a comprehensive overview of current evidence-based guidelines for familial hypercholesterolemia care, along with general and specific strategies for implementation [13▪,40▪]. The following section presents recent studies that have applied implementation science methods to improve the use of genetic testing for familial hypercholesterolemia.

BARRIERS AND FACILITATORS TO GENETIC TESTING FOR FAMILIAL HYPERCHOLESTEROLEMIA

Several studies have described barriers and facilitators to translating guidelines around the detection and management of familial hypercholesterolemia into practice [41,42,43▪,44▪▪,45]. In a systematic review by Hendricks *et al.* [42], barriers and facilitators to familial hypercholesterolemia genetic testing were mapped across the five domains of the Consolidated Framework for Implementation Science (CFIR) (Fig. 1). The CFIR domains include: 1) characteristics of the intervention, 2) outer setting, 3) inner setting, 4) characteristics of individuals, and 5) implementation process, and are used to guide the assessment of factors that influence the implementation of evidence-based guidelines [46]. Some of the barriers identified by Hendricks-Sturrup *et al.* [42], along with their respective domains (in brackets), include: the cost and convenience of genetic testing (characteristics of intervention), discrimination following a positive result (outer setting), poor reporting of family history (inner setting), genetic testing considered outside of provider scope of practice (characteristics of individuals), and that risk stratification and management are based on phenotype rather than genotype (process). Fahim *et al.* [47▪], also used the CFIR to investigate the barriers and strategies for implementing genetic testing, particularly for familial hypercholesterolemia. Similarly, Sarkies *et al.* [43▪], describe the barriers and facilitators to implementing guidelines for familial hypercholesterolemia detection, including the underutilization of genetic testing. The study engaged key stakeholders to identify the barriers and facilitators to implementing best practice and factors were identified at the patient, provider and system level. Using a mapping process, they explored the relationships between barriers and facilitators, which could then be used to inform the development of comprehensive implementation strategies. Although some countries have addressed a few of these barriers (i.e. cost and reimbursement for genetic testing are now subsidized by the Australian government under the country's universal health insurance scheme) several challenges remain across multiple levels and need to be addressed [48].

IMPLEMENTATION STRATEGIES TO IMPROVE THE USE OF GENETIC TESTING FOR FAMILIAL HYPERCHOLESTEROLEMIA

Implementation strategies are specific methods or techniques used to promote the adoption, integration, and sustainability of evidence-based interventions into practice [49]. Recent research has focused on developing and tailoring implementation strategies that address known barriers to the use of genetic testing for familial hypercholesterolemia. Literature reviews, key informant interviews, focus groups, and or engagement sessions with key stakeholders (i.e., patients, families, and healthcare providers) have been used to develop, refine, and optimize strategies at the patient, provider, and system level [8▪,9▪,44▪▪,50▪▪,51▪▪]. Implementation strategies that have been used to improve the use of genetic testing for FH include: 1) supporting the communication of an familial hypercholesterolemia diagnosis with at-risk relatives and 2) improving familial hypercholesterolemia detection in primary care.

STRATEGIES TO SUPPORT COMMUNICATION OF A FAMILIAL HYPERCHOLESTEROLEMIA DIAGNOSIS WITH AT-RISK RELATIVES

An important step for increasing familial hypercholesterolemia detection includes identifying at-risk relatives, a task commonly carried out by the first family member diagnosed with familial

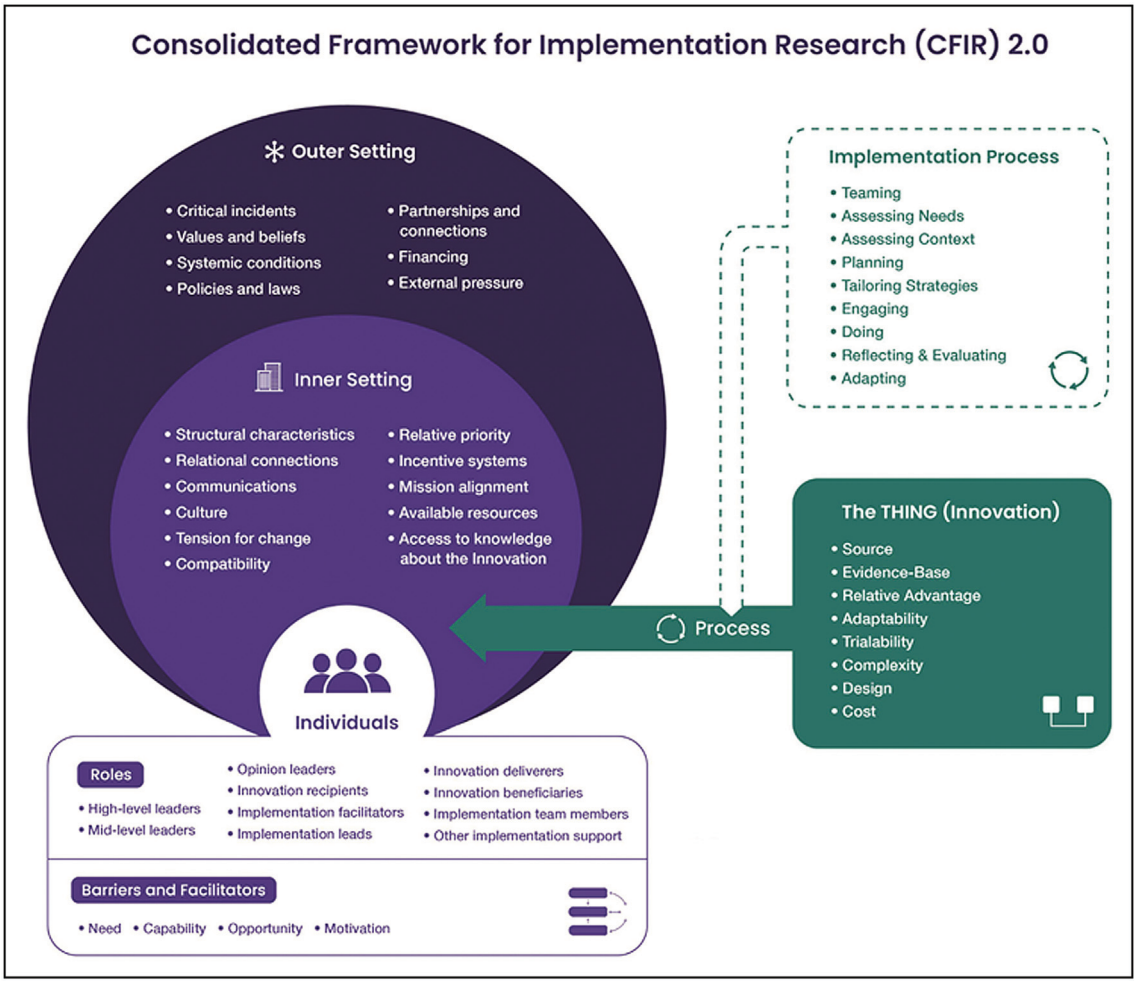

FIGURE 1. Consolidated Framework for Implementation Research (CFIR). Image adapted by the Center for Implementation https://thecenterforimplementation.com/toolbox/cfir and based on Damschroder LJ, Reardon CM, Opra Widerquist MA, Lowery J. 2022. Conceptualizing outcomes for use with the Consolidated Framework for Implementation Research (CFIR): the CFIR Outcomes Addendum.

hypercholesterolemia (i.e. referred to as the proband). This approach typically includes providing a family letter to the proband to pass on to their relatives, however, this method has shown little success [52]. The Identification, Methods, Patient Activation and Cascade Testing for FH (IMPACT FH) is a multistage study that examines the impact of communication strategies to improve the uptake of cascade testing [53]. As part of a patient-centred cascade testing program, the study utilized feedback from patients and their families to inform the refinement of three implementation strategies (i.e. a family letter, digital tools, or a direct approach by a healthcare provider) to communicate with relatives about familial hypercholesterolemia [50▪▪]. This study found offering different communication options is important and highlights the value of end user feedback in improving the success of cascade testing programs.

STRATEGIES TO IMPROVE DETECTION OF FAMILIAL HYPERCHOLESTEROLEMIA IN PRIMARY CARE

Two studies have focused on improving cascade screening within primary care [8▪,54]. In these studies, implementation science methods were embedded into the study design, which included a step-by-step approach to develop and refine implementation strategies to support primary care physicians in carrying out cascade screening. Implementation mapping is a step-by-step process used to develop and inform appropriate and effective strategies that are specific to the setting or context in which they will be applied [55]. Jones *et al.* [9▪], describe how implementation mapping can be used to develop strategies that address gaps in care across the familial hypercholesterolemia journey from diagnosis to management. This approach was used in the Collaborative Approach to Reach Everyone with Familial Hypercholesterolemia

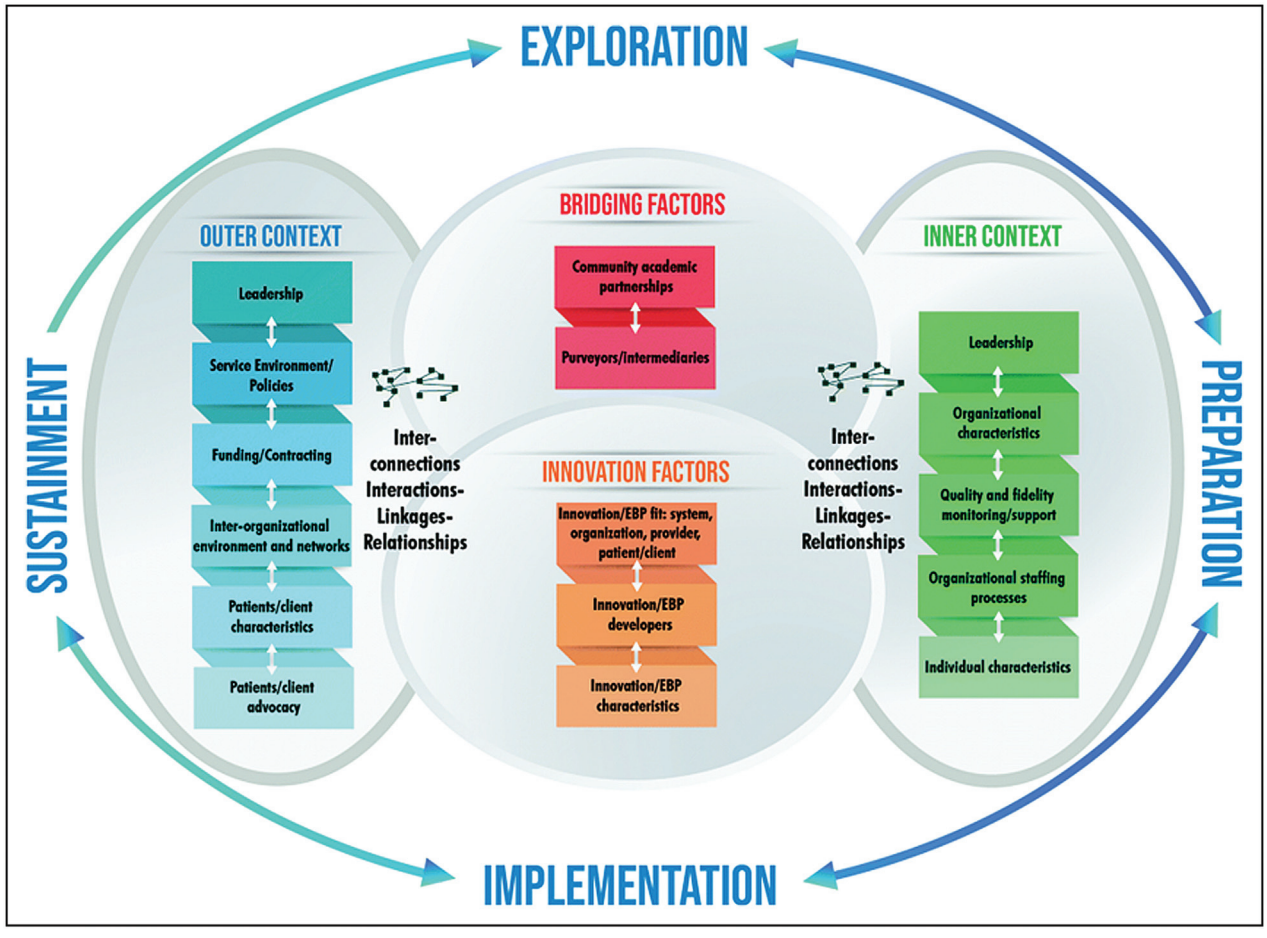

FIGURE 2. Exploration, preparation, implementation and sustainment framework. Image from Moullin JC, Dickson KS, Stadnick NA, Rabin B, Aarons GA. 2019. Systematic review of the Exploration, Preparation, Implementation, Sustainment (EPIS) framework. *Implement Sci* 14(1):1.

(CARE-FH) clinical trial aimed at improving familial hypercholesterolemia awareness, identification, and management in primary care [54]. Data were collected through interviews, clinical observations, surveys, and deliberate engagement sessions and were used to develop and refine an implementation strategy support package. The package included specific strategies focused on patient outreach, clinician education and training, clinician notification, and standardized screening documentation using electronic health record tools. Similarly, guided by the Exploration, Preparation, Implementation, Sustainment (EPIS) framework (Fig. 2), Birkenhead *et al.* [8▪], developed a primary–tertiary shared care model to increase cascade genetic testing in primary care. Cascade genetic testing is subsidized under the Medical Benefits Schedule (MBS) and can be ordered by general practitioners for patients who have a first-degree or second-degree relative with a confirmed pathogenic variant. In developing the model, a barrier to implementing guidelines for familial hypercholesterolemia care was a lack of awareness of familial hypercholesterolemia and the MBS Item [43▪]. As such, the model of care includes a stakeholder informed cascade testing package to advise general practitioners of the MBS item and how to undertake cascade genetic testing [8▪]. The package also includes the option of providing a saliva sample for genetic testing to help address barriers to sample collection that have previously been reported [42]. In both studies, clinician level barriers, including limited knowledge and time, were addressed by facilitating the ordering of genetic testing through step-by-step guidelines and education around familial hypercholesterolemia. Additional support to improve the use of genetic testing was provided through an information video [44▪▪] and a direct phone line to the tertiary clinic [8▪]. Strategies to improve capacity for general practitioners to undertake genetic testing are important as providers tend to prioritize diagnostic sensitivity aimed at catching as many potential familial hypercholesterolemia cases as possible, over specificity, which might lead to more false positives [56].

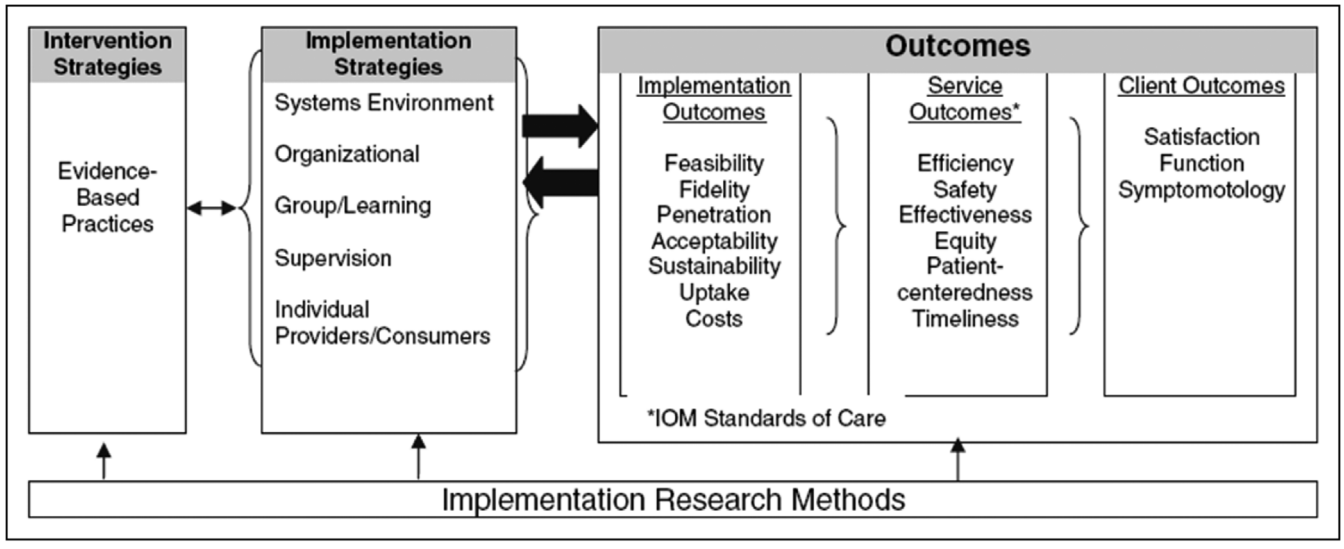

FIGURE 3. Conceptual model of implementation research (CMIR). Image from Proctor *et al.* [57].

OUTCOMES OF IMPLEMENTATION STRATEGIES TO IMPROVE THE USE OF GENETIC TESTING

The next phase involves implementing and evaluating the outcomes of implementation strategies when applied in real-world settings [8▪,53,54]. The Conceptual Model of Implementation Research (CMIR) describes implementation outcomes across three distinct categories: implementation/process outcomes, health service outcomes, and patient health outcomes (Fig. 3) [57]. Implementation outcomes are distinct from service (i.e. increase in genetic testing) or clinical (i.e. reduction in LDL-c) outcomes and reporting on all three is important to ensure the long-term effectiveness of a program. The CMIR was used in the IMPACT FH program, and positive implementation outcomes were reported [11▪▪]. For example, a communication strategy that helped relatives order a mail in genetic testing kit made is easier to complete the cascade testing. In relation to service outcomes, Jones *et al.* [58▪▪] found when probands selected at least one implementation strategy to communicate their familial hypercholesterolemia diagnosis with relatives, there was a significant increase in the uptake of cascade testing (i.e. relatives were more likely to undergo cascade testing if probands selected at least one of the three strategies). Furthermore, 25.7% (29/113) compared with 3.8% (1/26) of first-degree relatives had genetic testing when at least one strategy was selected. The study also reported that significantly more first-degree relatives (42.5 vs. 3.5%) completed genetic testing after the strategies were implemented. Probands were also more likely to choose a strategy (vs. no strategy) if they had an appointment with the genetic counsellor. Additionally, Morgan *et al.* [51▪▪], explored the impact of genetic counselling on genetic testing and found significantly more first-degree relatives completed cascade testing when the proband completed genetic counselling than probands who did not have genetic counselling. Within the primary care setting, preliminary findings (not yet published) have shown implementation strategies that support primary care physicians to carry out cascade screening can successfully increase genetic testing [59].

An important element of implementation science methods includes gathering input from end users who will be directly involved in implementing (or impacted by) the evidenced-based guidelines. This helps ensure engagement, support, and buy-in, and increases the likelihood of successful uptake. Studies that describe the barriers and facilitators to implementing evidence-based guidelines conclude that a structured and systematic implementation science approach is needed to ensure research outcomes reach those meant to benefit. The studies included in this review have all used this approach. Furthermore, a key element of all studies was tailoring or refining strategies based on input from stakeholders. This is a critical component of implementation science to ensure that interventions are effectively adapted to the specific context and needs of a target population, thereby enhancing the likelihood of successful and sustainable implementation.

CONCLUSION

Future research should prioritize detection through universal screening and integrating different implementation science approaches to help overcome

barriers to improve familial hypercholesterolemia care. Efforts should also focus on understanding the patient experience, a core element in improving outcomes. The unique challenges that exist at the patient, provider, and system levels within healthcare highlight the need for innovative solutions that are not only specific and tailored, but also adaptable, to ensure success. Implementation science can help identify and address these challenges and reduce the long-standing gaps in familial hypercholesterolemia care.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

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This study protocol was included as it uses an implementation science study design to evaluate a model of care to support increased cascade genetic testing for familial hypercholesterolemia in primary care. Although final outcomes from the study are not yet available, preliminary findings show the model has increased the use of genetic testing by primary care physicians (unpublished data).

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This study was included as it is the first to use a systematic implementation science approach to address gaps in familial hypercholesterolemia care by mapping interventions to specific implementation strategies across the care pathway from familial hypercholesterolemia detection, genetic testing, and management to improve familial hypercholesterolemia care.

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This is an important article highlighting how implementation science methods can help bridge the evidence to practice gap in the use of genetic testing for familial hypercholesterolemia. The article emphasizes that future efforts to build on evidence need to incorporate implementation science to ensure knowledge gained is applied in practice.

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This study describes the barriers and facilitators to implementing guidelines for familial hypercholesterolemia detection, which includes the use of genetic testing. The study incorporated an important element of implementation science by engaging key stakeholders in the process of identifying barriers and facilitators to implementing best practice, a first step in addressing gaps in familial hypercholesterolemia care.

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This study shows how implementation science can be used to develop a stakeholder informed implementation strategy package aimed at improving familial hypercholesterolemia care. Although the impact of the implementation strategy package (e.g. includes one strategy aimed at increasing the use genetic testing for familial hypercholesterolemia) are not yet available, this study provides a clear example of how implementation science methods were used to develop specific strategies that were informed by end users to address identified barriers and, therefore, are more likely to be effective in increasing the use of genetic testing.

45. Kinnear FJ, Wainwright E, Perry R, *et al.* Enablers and barriers to treatment adherence in heterozygous familial hypercholesterolaemia: a qualitative evidence synthesis. BMJ Open 2019; 9:e030290.
46. Damschroder LJ, Reardon CM, Widerquist MAO, Lowery J. The updated Consolidated Framework for Implementation Research based on user feedback. Implement Sci 2022; 17:75.
47. ■ Fahim SM, Alexander CSW, Qian J, *et al.* Current published evidence on barriers and proposed strategies for genetic testing implementation in healthcare settings: a scoping review. J Am Pharm Assoc 2023; 63:998–1016.

This scoping review was included as it highlights the lack of information available on how to implement genetic testing into clinical settings. It provides a useful summary of the current evidence on barriers to and strategies for integrating genetic testing into healthcare settings, including testing for familial hypercholesterolemia. The implementation barriers and suggested strategies described in this article are useful in supporting the integration of genetic testing across various healthcare settings.

48. Birkenhead K, Sarkies MN, Sundercombe S, *et al.* Familial hypercholesterolaemia: improving the health of individuals and families. Med Today 2024; 25 (6 Suppl):15–20.
49. Proctor EK, Powell BJ, McMillen JC. Implementation strategies: recommendations for specifying and reporting. Implement Sci 2013; 8:139.
50. ■■ Campbell-Salome G, Jones LK, Walters NL, *et al.* Optimizing communication strategies and designing a comprehensive program to facilitate cascade testing for familial hypercholesterolemia. BMC Health Serv Res 2023; 23:340.

This study is of importance as it utilized feedback from individuals and families to inform the refinement of three previously developed implementation strategies (i.e. a family letter, digital tools, or a direct approach by a healthcare provider) to communicate with relatives about familial hypercholesterolemia as part of a patient-centred cascade testing program. This study clearly describes how implementation science was used to ensure stakeholder feedback was incorporated into program design.

51. ■■ Morgan KM, Campbell-Salome G, Walters NL, *et al.* Innovative implementation strategies for familial hypercholesterolemia cascade testing: the impact of genetic counseling. J Pers Med 2024; 14:841.

This study follows the IMPACT FH study and specifically reports on the impact of genetic counselling on medical outcomes, the selection of a communication strategies, and the uptake of genetic testing. The study highlights the value in genetic counselling in improving outcomes. Specifically, more first-degree relatives completed cascade testing when probands completed genetic counselling than those who did not complete genetic counselling.

52. Dheensa S, Lucassen A, Fenwick A. Limitations and pitfalls of using family letters to communicate genetic risk: a qualitative study with patients and healthcare professionals. J Genet Couns 2018; 27:689–701.
53. Campbell-Salome G, Jones LK, Masnick MF, *et al.* Developing and optimizing innovative tools to address familial hypercholesterolemia underdiagnosis: identification methods, patient activation, and cascade testing for familial hypercholesterolemia. Circ Genom Precis Med 2021; 14:e003120.
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This study was included as it uses communication strategies, informed by implementation science methods, to increase cascade testing. Findings are particularly relevant as they demonstrate that the application of implementation science in program design can successfully improve the use of genetic testing.

59. Birkenhead K, Sullivan D, Trumble C, *et al.* Preliminary results from the implementation of a primary-tertiary shared care model to improve the detection of familial hypercholesterolaemia (FH): a mixed methods pre-post implementation study. Heart, Lung and Circ 2024; 33:S315.