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RESEARCH

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A qualitative study of perceptions of the care pathway for familial hypercholesterolemia: screening, diagnosis, treatment, and family cascade screening

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Abstract

Background Familial hypercholesterolemia (FH) is an autosomal dominant genetic condition that carries increased risk for premature atherosclerotic cardiovascular disease, cardiovascular events, and death. Due to low uptake of evidence-based practices, up to 80% of FH patients remain undiagnosed and most are undertreated. This project aimed to understand patient and clinician perceptions across the care pathway of evidence-based diagnosis and treatment of FH, to inform implementation strategy design for two clinical trials seeking to increase evidence-based care.

Methods With input from FH experts, we identified key points along the FH care pathway that might be targeted with broad-scale implementation efforts, including: (a) identification of the need for screening; (b) completion of screening test(s); (c) diagnosis; (d) connection to treatment; and (e) family cascade screening (a process used to identify and screen relatives of individuals diagnosed with FH). Then, we conducted qualitative interviews with patients who had participated in a prior FH quality improvement initiative and with clinicians who treat high cholesterol. We analyzed data using thematic analysis.

Results We interviewed 21 patients and 17 clinicians. Patient themes offered insights related to the impact of family history, reactions to a diagnosis of high cholesterol and/or FH, experiences with FH treatment and clinical care, perceptions of tools to diagnose FH, motivations and preferences for FH screening efforts, and reactions to family screening. Clinician themes offered insights into the perceived value of FH screening and diagnosis, current FH-related practice and context, and attitudes toward tools to aid clinical practice. In both sets of interviews, confusion and misconceptions about what makes FH unique and its clinical implications were common, as were concerns about logistics and competing priorities.

Conclusion Qualitative inquiry generated insights into several modifiable patient and clinician determinants of engagement with evidence-based implementation along the FH care pathway, many of which can be targeted with behavioral economics strategies that simplify complex decisions and by addressing informational and emotional needs. These findings offer actionable insights to inform future implementation research that seeks to close the evidence-to-practice gap in diagnosis and delivery of evidence-based care for FH.

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Keywords Familial hypercholesterolemia, Barriers to care, Underdiagnosis, FIND FH, Cascade screening, Machine learning, Care pathway, Implementation science

Contributions to the literature

- We identified key steps along the familial hypercholesterolemia (FH) care pathway to inform investigation of opportunities to increase implementation of evidence-based practices for identification and treatment of FH.
- Interviews with patients and clinicians identified several modifiable determinants of implementation related to evidence-based practices for FH including initial identification and diagnosis, adequate treatment, and family screening for FH, particularly those related to knowledge and logistics.
- Study findings suggested that both patient-facing and clinician-facing strategies are needed and informed development of implementation strategies for two clinical trials seeking to increase evidence-based care for FH with insights from behavioral economics.

Background

Familial hypercholesterolemia (FH) is a genetic disorder of cholesterol metabolism that is estimated to affect 1 in 313 people internationally and 1 in 250 people in the United States [1–3]. FH causes lifelong elevation of low-density lipoprotein cholesterol (LDL-C), generally over 190 mg/dL in adults and 160 mg/dL in children [1]. Because of its unique features, evidence-based screening and treatment approaches for FH differ from those for other types of high cholesterol in four key ways. First, early diagnosis and intervention are critical because elevated LDL-C begins at birth and leads to substantially increased risk for premature atherosclerotic cardiovascular disease (ASCVD) [1]. Second, FH does not respond adequately to lifestyle interventions and needs early and ongoing pharmacological management, often beginning in childhood [4, 5]. Third, individuals with FH typically require higher dosages or combinations of lipid-lowering therapies and closer monitoring to bring LDL-C to safer levels [1]. Fourth, because FH is typically caused by gene mutations that follow an autosomal dominant pattern (i.e., first-degree biological relatives have a 50% chance of having inherited FH), family cascade screening–or identifying and screening the family members of a diagnosed individual, beginning with parents, siblings, and children as early as age 2–has been found to improve timely diagnosis and reduce morbidity in several countries [6].

In recognition of both the need for FH-specific approaches to care and the fact that early diagnosis followed by proactive, intensive treatment can prevent or delay the onset of ASCVD and dramatically reduce morbidity and mortality [7], the American Heart Association, American College of Cardiology, American Academy of Pediatrics, and others have issued guidelines for FH screening and treatment [8, 9]. Family cascade screening for FH has also been deemed a Tier 1 genomic application with Grade A evidence-based recommendations by the Centers for Disease Control and Prevention [10]. Yet up to 80% of individuals with FH remain undiagnosed and half of those who are identified are undertreated [7]. Diagnostic and treatment delays are also common; a cross-sectional analysis of data from the national Cascade Screening for Awareness and Detection of FH (CASCADE FH®) Registry found that among 1,295 patients from 11 U.S. lipid clinics, median age at time of FH diagnosis was 47 years [11]. These missed opportunities for risk reduction have devastating consequences: without effective treatment, up to one quarter of individuals with FH will have a cardiac event by age 40—with 7% of them being fatal [1]. This represents an approximate 100-times greater mortality risk from cardiovascular disease compared to the general population. Unfortunately, available ASCVD risk calculators (which use age as a major input) underestimate risk in individuals with FH [12, 13], and FH diagnosis often occurs only after a cardiovascular event.

Prior research has documented multi-level barriers to evidence-based identification and treatment of FH in routine practice [14, 15]. Clinician-level determinants are a major barrier to implementation of FH guidelines [16, 17]; for example, surveys of primary care providers in the U.S. have found a disconnect between high perceived importance of early intervention for cardiac risk and actual (low) rates of lipid screening and FH evaluation [16, 18]. Additionally, in keeping with research on the limited integration of genetics into primary care [19], studies in multiple countries and practice settings have found substantial knowledge gaps related to evaluation and treatment of FH and room for improvement in FH screening rates [16–18, 20–22]. After FH diagnosis, patient barriers such as medication access and costs, medication-related beliefs (e.g., misconceptions about the importance of lipid-lowering drugs), and adherence challenges can interfere with optimal treatment [23–26].

Lastly, common approaches to family screening in the U.S., such as provision of a "Dear Family" letter to notify individuals of their relative's FH diagnosis and the need for screening, have had disappointing results [27, 28]. In recent years, there have been multiple efforts to develop new approaches to implementation of evidence-based practices (EBPs) for FH in the U.S., many of which are ongoing [29–31].

Study Objective

Our objective was to interview patients and clinicians to solicit their perceptions of the care pathway for FH, in order to gain insight into opportunities to centralize, automate, or otherwise support more consistent implementation of evidence-based FH care within our target health care system. This inquiry represented the first step in our efforts to obtain constituent feedback to inform development of new implementation strategies for two hybrid effectiveness-implementation trials. The first hybrid trial is focused on a population-based approach to initial FH screening using an evidence-based machine learning tool called Flag Identify Network and Deliver FH (FIND FH®). Developed by the Family Heart Foundation—a nonprofit research, advocacy, and patient education organization for FH and elevated lipoprotein(a)—the tool has been trained to look for patterns in data, using several hundred variables available in electronic health records (EHRs) [32]. It quantifies the relative likelihood of an individual having a clinical profile similar to someone with FH and has been shown to identify those at greatest risk for FH with 84% accuracy [33, 34]. A pilot study of the FIND FH tool found that only 7.1% of individuals flagged as having an elevated risk of FH went on to complete genetic testing and clinical consultation, indicating a need to optimize implementation strategies to increase the number of identified patients who complete the diagnostic process and initiate or intensify treatment. The second trial is focused on family cascade screening and seeks to adapt components of approaches used successfully in the Netherlands (e.g., direct outreach to relatives, involvement of a patient advocacy foundation), to increase feasibility in the U.S. [35] while navigating national barriers such as geographic and emotional distance within families, medical privacy laws, and lack of a routine way for disparate clinical teams to connect or share records. Both of the trials seek to combine constituent feedback with principles from behavioral economics, a field that offers insights into cognitive biases affecting decisions and outlines how to harness "choice architecture" to simplify complex decisions and nudge individuals toward desired behaviors. It has been shown to be useful in shifting clinician and patient behavior toward evidence-based care and can be especially helpful in cases where complexity contributes to a gap between intention and action [36–39].

Methods

Setting and Participants

This study was conducted within the University of Pennsylvania Health System ("Penn Medicine"), which includes six hospitals and approximately 100 community-based practices located in urban, suburban, and rural areas in and around Philadelphia. Penn Medicine serves a racially, ethnically, and socioeconomically diverse population. Participants were drawn from purposive samples of patients and clinicians.

Patient sampling

We identified individuals who had participated in a prior (2018–2019) Penn Medicine quality improvement initiative that used the FIND FH machine learning tool to identify high-risk patients and offered them free genetic testing for FH and a results review visit with an FH expert [34]. The prior study team shared a list of patients and clinicians to facilitate our outreach. We applied the following patient participant eligibility criteria: (1) under 75 years of age; (2) had originally been flagged by the FIND FH tool as having elevated risk for FH; and (3) had subsequently been seen by a clinician affiliated with the Penn Medicine Preventive Cardiovascular Program who did not object to their patients being contacted for recruitment. Penn Medicine policy allows researchers to issue study invitations unless the patient has requested not to be contacted for research purposes. In an effort to solicit broad perspectives, we initially selected individuals from the full prior participant list at random and did not require them to have received an FH diagnosis during their evaluation. Later, we shifted to purposive sampling of individuals who also had an FH diagnosis in their EHR, to ensure sufficient respondents (and richness of response) for interview questions inquiring about care pathway steps following FH diagnosis.

Clinician sampling

We obtained a list of clinicians who were involved in the same quality improvement study (i.e., physicians with a focus on family medicine, internal medicine, and cardiology) who were still active at Penn Medicine. We initially contacted clinicians in random order. We also asked early participants to identify colleagues who might be interested in participating, via a snowball sampling approach, in order to increase our ability to recruit busy clinicians.

Care Pathway and Interview Guide Development

To guide development of our implementation strategies and focus our inquiry, we consulted FH experts and

outlined a multi-step "FH care pathway" (Fig. 1) to capture key points in the identification and treatment of FH. First, individuals at elevated risk should be identified as candidates for FH diagnostic evaluation, at either the individual level or via a population-based approach that screens large groups of people. Each person identified as being at risk should receive appropriate testing and evaluation, typically consisting of genetic testing, lipid testing, or both along with a review of medical history, medications, family history, and physical exam findings. Results should be interpreted using standardized clinical criteria (e.g., Dutch Lipid Clinic Network Criteria [40–42]) to either rule out FH or identify Possible, Probable, or Definite FH. Next, results must be communicated to

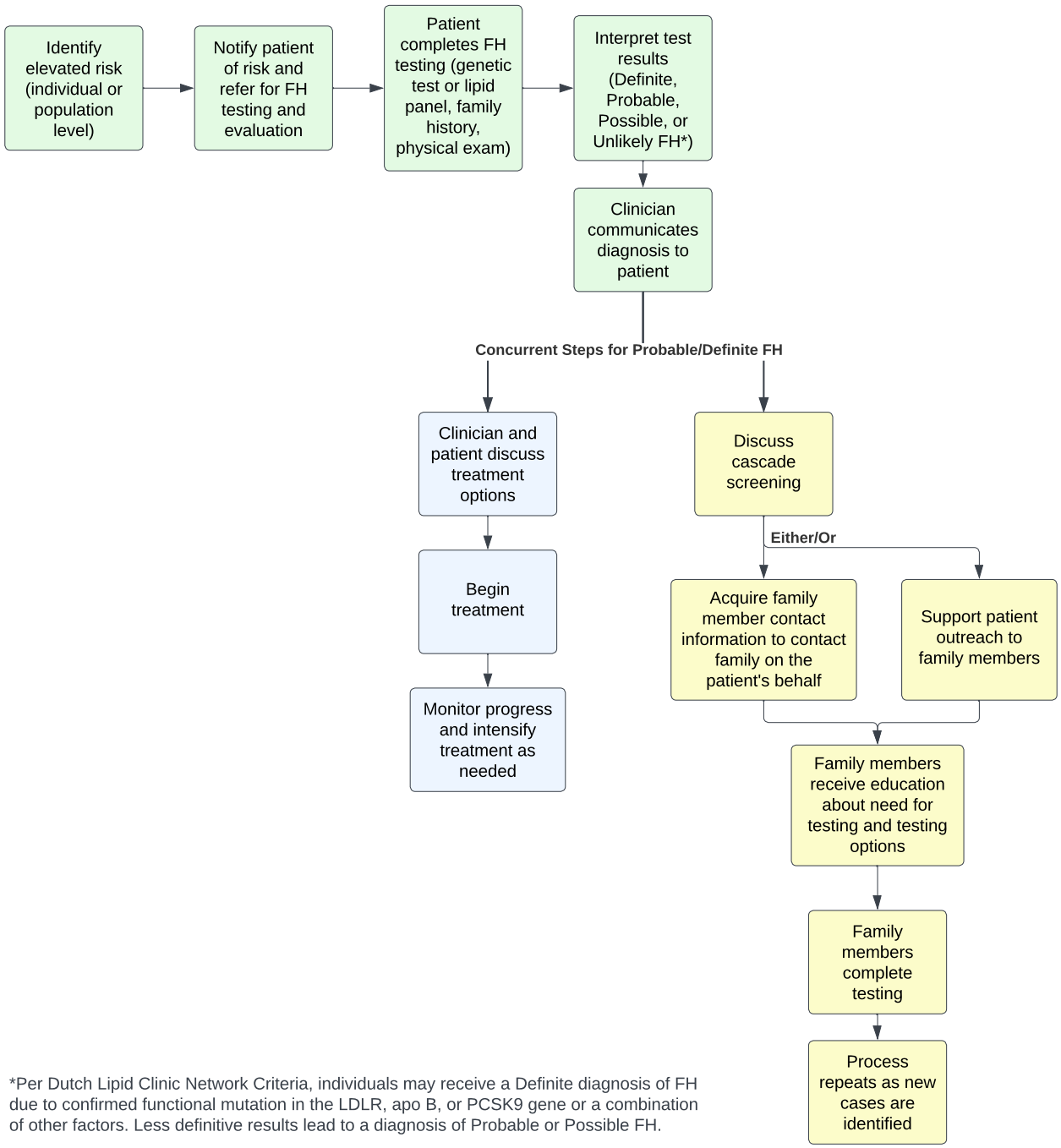

Fig. 1 Care Pathway for Familial Hypercholesterolemia (FH)

the patient. When FH is diagnosed (i.e., a "proband" is identified), two pathways to evidence-based care commence in parallel: proband treatment (i.e., discussion of recommended options, treatment initiation, monitoring of adherence and response, and intensification of treatment as needed) and family cascade screening (i.e., outreach to relatives by the proband, clinician, or a third party and initiation of screening).

To gain additional specific insights into obstacles and opportunities along the care pathway, we sought to assess informational and practical needs as well as perceived acceptability, appropriateness, and feasibility of various implementation approaches. The patient interview guide included questions about patient understanding of their own high cholesterol and family history; familiarity with the term familial hypercholesterolemia or FH and its implications for treatment; preferences for communication from their health system; preferences related to the process of FH diagnosis, including feedback on the FIND FH tool; willingness to contact family members or share family members' contact information as part of cascade screening efforts; perceived willingness of family members to be tested; and thoughts on medication initiation, adherence, intensification, and lifestyle changes. The clinician interview guide included questions about caseload and patient population; typical cholesterol screening practices; familiarity with FH and comfort making a diagnosis; perceptions of whether and how an FH diagnosis should influence treatment; perceived personal and patient facilitators and barriers to FH diagnosis, treatment, and family screening; and reactions to potential strategies for centralized implementation of EBPs for FH (e.g., the FIND FH tool and how it could be integrated into their practice, preferences for communicating with patients about FH). We also collected demographic information from both patients and clinicians.

We iteratively updated and refined the patient interview guide as interviews progressed. We piloted the clinician interview guide with two clinicians who are familiar with FH; those data were not included in the analysis.

Procedures

Study procedures were approved by the University of Pennsylvania Institutional Review Board and we have followed the Consolidated Criteria for Reporting Qualitative research (COREQ) checklist [43].

To recruit patients and clinicians, we sent an initial email followed by as-needed reminder emails after 3, 6, and 13 days (including weekends), for a maximum of four contact attempts. Individuals who expressed interest in participating in a qualitative interview were contacted by the study team. Recruitment continued until no new emergent themes arose after 3 consecutive interviews (for patients) [44] or until all eligible individuals had been contacted (for clinicians).

One-time individual interviews were conducted from January 2022 through July 2022, via phone for patients and videoconference for clinicians. Interviewers were female research coordinators (MM, JS, KS) with either master's degrees or some graduate-level education as well as training in qualitative interviewing. Interviewers did not have relationships with participants prior to the interview, and the interview guide was not shared with participants beforehand. Interviewers reported their job titles and study goals to participants and obtained verbal informed consent. Interviews lasted approximately 30 min and were digitally recorded with participants' permission. Interviewers wrote field notes after every interview. Audio recordings were professionally transcribed and loaded into Atlas.ti software.

Data Analysis

Patient data

Analysis was guided by the steps in the care pathway that were defined a priori. We also identified additional concepts that emerged from the data (i.e., inductive analysis). After initial exploration of data, a comprehensive code book was developed and applied to all patient interview data [45]. A sample of transcripts were coded separately by two coders and compared to assess coding consistency, with discrepancies resolved by consensus. Patient transcripts were analyzed by an interviewer (JS), a female master's-level team member (RCK), and a female doctorate-level researcher (TK). When coding was completed, the research team developed theme sheets and then conducted comparative thematic analysis [46, 47] to identify perspectives that might influence engagement with EBPs and implementation strategies. Potential interventions to address these perspectives were also considered and are discussed below.

Clinician data

For clinician transcripts, data were consistent across the majority of responses. Rather than line-code the data, we conducted rapid thematic analysis [48, 49]; multiple people reviewed transcripts and discussed emergent themes.

Participants were not asked for feedback on transcripts nor study findings.

Results

Sample Characteristics

Twenty-one of 67 invited patients (31.3%) and 17 of 135 invited clinicians (12.6%) completed an interview. Reasons for patient non-participation included: no response to recruitment attempts ($n=39$), responded to a recruitment message but not to interview scheduling attempts

($n=3$), age under 18 ($n=1$), and self-report that they did not have FH ($n=2$). One patient agreed to participate but decided to end the interview after the first question, stating that they didn't know if they had high cholesterol. Reasons for clinician non-participation included: no response to recruitment attempts ($n=108$), declined to participate ($n=8$), incorrect email address ($n=1$), and clinician became part of the study team ($n=1$).

The patient participant group had a mean age of 58.5 years (SD = 14.3). Three (14.3%) were under 40 years of age, 7 (33.3%) were aged 40–59, and 11 (52.4%) were 60 or older. The majority were white and non-Hispanic ($n=19$; 90.5%), and more than half were male ($n=13$; 61.9%). All annual household income categories were represented (from below $30,000 to over $250,000), with half of the participants in the highest income categories (i.e., $100,000+). The clinician participant group had a mean age of 45.3 years (SD = 8.9), with an average time in medical practice of 18.2 years (SD = 8.9). Most clinician participants were white and non-Hispanic ($n=11$; 64.7%) or Asian or Asian American ($n=5$, 29.4%), and just over half were female ($n=9$; 52.9%). Most were in a primary care specialty (i.e., internal medicine, family medicine); one hospitalist and one interventional cardiologist also participated.

Patient Themes

Patient themes included the impact of family history, reactions to a diagnosis of high cholesterol and/or FH, experiences with FH treatment and clinical care, perceptions of tools to detect FH, motivations and preferences for FH screening efforts, and reactions to family screening. Table 1 includes sample quotes from identified themes and subthemes.

Impact of family history

Most respondents reported a family history of elevated cholesterol, and many reported a family history of cardiovascular events. Some noted their family history had led to a sense of fatalism and fear regarding their own health. Others stated that it served as a motivator; multiple participants referenced specific family health events that inspired them to engage in steps to avoid going through similar difficulties themselves. In some cases, this was especially true as they approached the age that their relative had been at the time of a cardiovascular-related death. Several participants cited lifestyle factors, such as eating habits, as a likely contributor to high cholesterol and heart disease in their families. One participant noted that they were not aware of a family history of high cholesterol until their own diagnosis.

Reactions to a diagnosis of high cholesterol and/or FH

In a few cases, participants recalled being diagnosed with high cholesterol in adolescence. Many reported finding out about their high cholesterol during a routine blood test or screening, and it was common for this to have occurred many years before they learned about FH specifically. Individuals expressed a variety of emotions about FH, including fear, anxiety, and guilt (especially in regard to eating habits); relief, gratitude, and commitment to a healthy lifestyle; and a sense of regret that their condition had not been identified sooner, especially if they had blamed themselves for their high cholesterol, had been frustrated when dietary changes and initial medication treatment hadn't worked, had believed living a healthy lifestyle would be enough to protect their heart, or had already required cardiac intervention.

Although participants were selected for interviews due to their involvement in a prior quality improvement study for individuals at high risk for FH, many expressed difficulty remembering the details of their involvement in that study or what they were told about their FH status. This occurred with individuals who did and did not receive a diagnosis of FH after being flagged by the FIND FH algorithm. Confusion about the implications of an FH diagnosis and how it differs from general high cholesterol was also common. Post-hoc analyses revealed that half of the participants who had an FH diagnosis in their EHR reported knowledge of this diagnosis, whereas the other half reported confusion about whether they had FH or reported a belief that they did not have FH. Many participants expressed a desire for more information about the condition and its treatment.

Experience with FH treatment and clinical care

Several individuals reported receiving conflicting messages from different health care providers about the seriousness of their high cholesterol; more than one participant noted that the onus is on the patient to reconcile various pieces of advice because different specialists are not communicating with one another. Participants also noted limited availability of FH specialists and long waits for appointments, as well as insurance and cost barriers in accessing FH medications, particularly PCSK9 inhibitors (a class of specialty drugs approved for patients with FH and/or clinical ASCVD who require additional lipid-lowering therapy). Whereas some participants expressed reservations about medications, several expressed a clear understanding of the link between their FH diagnosis and a need for medication and described how this motivated them to adhere to their doctor's treatment recommendations. Many participants reported trying several types of

Table 1 Selected Patient Quotes

Themes and Subthemes	Quotes
Impact of Family History	
Fatalism/Fear	*So my father had his first heart attack, and he was in his early 40s – high cholesterol. And he passed away – he wasn't even quite 70 – which for me, that's somewhat scary…I'm getting close to that age too. (2014)*
	I fear that I'm just going to drop one day like my dad did. (2940)
Motivation	*…when my dad had triple bypass, I remember saying [to my internist]…please, I never ever want my ribs broken in order to be able to do a triple bypass. What do I need to do so that never happens to me? (2093)*
Lifestyle factors	*…we lived on round steak, and hamburgers, and cookouts, and beer, and clams. (2134)*
Lack of knowledge of family history	*I don't know that we all know our family histories well enough to provide the correct information that would screen for this thing. Because I didn't know until I found out I had high cholesterol and then asked my mom … it wasn't that I was flagged for having history…I didn't probably talk about that in my history and physical when I first went to my PCP. (2016)*
Reactions to Diagnosis of High Cholesterol and/or FH	
Emotional reactions	*I think I felt better…the way it was being explained to me felt – made me feel like it wasn't – I didn't do it to myself, basically, that I didn't cause my high cholesterol [with lifestyle]. (2016)*
Lack of memory for diagnostic evaluation	*I don't really – like I said – remember too many of the specifics. Because it was – it's not sticking out in my brain, I assume that it went pretty smoothly and fine. (2007; no FH diagnosis in medical record)*
	I mean, I don't even know if I'm officially diagnosed with that, but I think that I – first I ever heard of it was that initial genetic study. (2123; FH diagnosis in medical record)
	…does FH stand for family history? (2060; FH diagnosis in medical record)
Desire for more information and action steps	*…like I said, just a little bit more information on what that meant. Now I'm diagnosed with this gene, does it change anything? Do I have to look out for anything else? Does it impact anything? I think just a little bit more information on what now? What do I use this information for? (2141)*
Experiences with FH Treatment and Clinical Care	
Conflicting messages and lack of care coordination	*I did ask my other doctors, what did they think, did I need to go on a statin? And they told me no. […] my biggest concern was the failure to communicate […] you could at least cc'd primary care, cardiology […] so that all the doctors are on the same page […] you can't have one group saying you don't need it and another group saying yes, you do. (2075)*
Increased understanding of etiology and implications for treatment	*…they screened…and [my young child's] cholesterol levels were in the 200s. And I remember saying, I couldn't have ruined him with food at this point. This has to be something that's family related. (2001)*
	And I've always run, I've always swam… So in my own mind, I thought that any heart disease that I might have would be addressed through all my exercise. Little did I know that you can do all of that, but still have heart disease. … So I realized I had to do much more than what I was doing. (2093)
	…like managed with medication I guess would be the goal. Because even if lost – like my understanding from my cardiologist is I could lose like – you know, I could lose 100 pounds, I'd still have high cholesterol. So it's – although it's beneficial and I should exercise and eat healthy just for my overall health, it's not the – it's not the thing that's going to like cure this or make this go away. (2016)
Treatment motivation	*…[my FH diagnosis] gave me the okay to be like, all right, now I know why I need the medication and why the medication is imperative. And it's not only the food and the exercise that I have to worry about, just making sure that I am sticking to the medication and things because it seems to be the only thing that is helping to bring that cholesterol down and keep it at a healthy level. (2141)*
	That's kind of what I took out of it if that makes sense. So let's be more careful, and let's find a treatment that works instead of just giving up on that. (2014)
Logistical barriers	*But even so, even with a prescription plan…I'd be paying $500 a month, or more [for the PCSK9 inhibitor]. And I couldn't afford that because I'm on a fixed income. (2134)*

Table 1 (continued)

Themes and Subthemes	Quotes
Perceptions of Tools to Detect FH	
Prevention	*Again, because [with the FIND FH tool] you can proactively find people based on other data bits that just might be missed. And if you can refer someone or get them into a treatment – they might not need – or it normally wouldn't have been noticed until there's already damage. I mean, that sounds like a pretty big win to me. So yeah, that's why – I – being able to be proactive and solve a problem before it's a problem seems pretty smart to me. (2014)*
	And I think that's an important part today, people, if they can get them early, with high cholesterol. I think you can save a lot of lives if you can get it early. (2940)
Equity	*…for the early times when we weren't sure why my cholesterol was so high and [diet modification and a statin] wasn't working, I think it would have answered a lot of questions a lot earlier. So I think it would be good just so that you can catch those people early. Because especially with women, the signs and symptoms [of heart attacks] are not the same for everyone. And people are getting them earlier and earlier. And I think being able to catch this, even though it's not getting heart disease, but it can lead to that, I think catching it as early as possible. And just getting a watchful eye and making sure that those people are medicated or doing the correct things earlier could help down the road. Instead of trying to catch somebody in their late 30s, early 40s when the damage is already done, it will take longer to take care of them. So I think it'd be great. (2141)*
	Well that way people that don't know that they have it – some people don't know what their family history is, so that would be nice if they could let them know ahead of time, that way they could get treatment. (2113)
Integration of technology into clinical care	*Oh, I think it's a good idea, as long as it's not used as the complete answer. Basically, yes, it's right. It should be a screening tool to get you into your doctor. (2098)*
	I think it's great. Anything that can add to someone's diagnosis or knowledge is valuable… Just additional information. More information is always helpful as long as you have somebody that comes and helps you understand it. (2093)
Privacy	*I know there are some that are probably worried about privacy concerns with that. But I think the healthcare benefits still far outweigh that. So I think it makes a whole bunch of sense, yes. (2014)*
Motivation and Preferences for FH Screening Efforts	
Health concerns	*I mean I was scared I was going to like drop dead of a heart attack, so I wanted to figure out what was going on. (2016)*
Access to experts	*And bluntly, I didn't think my primary was giving me enough information on this. I felt like I could be doing more.[…] …and an opportunity to learn more about this and to work with a group that that's all they do – I kind of jumped at the opportunity… (2014)*
Impact on family	*I just said yes because I was interested because of my mother's really, really high cholesterol, I was very interested is this something I'm passing down to my kids. (2131)*
Reactions to Family Screening	
Family dynamics	*They would receive it very, very well. I'm often telling [my siblings] what they need to do, based upon my situation.[…] …we all love each other. We're good friends. […] And we're all – we sit down, we talk about so what are your levels this month and things like that. (2093)*
	I don't know. I don't discuss family members' medical history. (2075)
Communicating risk	*[My doctor] couldn't reach out because he doesn't have a relationship with them, so I did. But parents, sometimes you just can't – lead a horse to water. But I told them that they have a tendency with same problem I have, and they should consult with their physicians. They said they talked to their physicians and their physicians didn't think it was a big deal at their age or with the numbers they had. (2940)*
	But if they were to receive something from a medical organization suggesting that they get some kind of testing, maybe they would take it more seriously. (2032)
Information needs	*Perhaps a website that they could go to, that you could refer them to, where they could read about it and why it would be necessary for them to be tested (2060)*
	And let me give them a piece of paper or a pamphlet explaining it. That would be really helpful, because it's someone that you love, that you care about, that's in your family that's going through it and that makes it all the more pertinent for them to listen to and want to do something about it. As opposed to someone off the street just handing you a flyer. (2093)

Table 1 (continued)

Themes and Subthemes	Quotes
Logistics	*I mean, probably time, just going in for an appointment. If it's something that could be done with just giving them a lab slip, I think that would be the easiest. But if they had to go make an appointment and see someone, and then go get blood drawn, I think that might be a barrier. (2123)*
	And also which family members we're talking about here. So if you just say, family members, people don't know, is it my siblings, is it my children, is it my cousins? What level of screening are you trying to achieve? And the other problem these days with some of that is families tend to be geographically dispersed, so you may be recommending screening for someone who lives in another part of the country or another part of the world. So the context of risk is important there because you don't want to create a lot of fear for people if it's not warranted. They can't get access to care easily. (2143)
Managing third-party outreach	*I would do it first because I wouldn't want to give out their personal telephone numbers, addresses or whatever to a third party. (2075)*
	…it probably would have to come from me, otherwise they'd just think it was spam, so. (2017)

medications and changing medications, often due to lack of efficacy or adverse effects. In regard to monitoring cholesterol, several participants expressed a preference for getting blood work before an appointment, rather than after, so they could talk to their clinicians directly about the results.

As a group, patient participants were open to a variety of modalities for receiving medical information and communicating with their medical team, including in-person appointments, telehealth visits, use of a patient portal, and email, phone, and text messages, but preferences varied among individuals; one individual suggested that obtaining preferences for follow-up modality could be helpful to ensure messages are not accidentally ignored. Similarly, whereas some participants had a clear preference for receiving health information from their personal doctors, others were open to receiving information from a variety of clinicians or other trained professionals and emphasized that quality of information and access to information was most important.

Perceptions of tools to diagnose FH

Many participants were enthusiastic about the idea of an automatic screening tool like FIND FH, due to its potential to improve early identification and prevention efforts. Individuals with FH noted that earlier identification would have allowed them to take preventive measures and saved them from disappointment when lifestyle modification or initial medication treatment was not sufficient to control their high cholesterol. Several participants noted that use of tools like FIND FH could help identify people at risk of cardiovascular health disparities, such as women and individuals who do not know their family history. Participants also noted the importance of being able to ask questions at the time of a new diagnosis and of coordinating use of centralized tools with their personal health care team.

Motivation and preferences for FH screening efforts

When asked about their motivations for participating in FH screening efforts, participants cited facilitators including a wish to increase their knowledge about health, intellectual curiosity, concern about their own health and the health of their relatives (especially their children), being asked at a time when health concerns were top of mind, the program's affiliation with specialists at a university-based medical center, altruism and a wish to contribute to new knowledge about FH, and free access to testing.

Reactions to family screening

No participant recalled formal family screening efforts following their FH diagnosis, but many supported the concept. Family dynamics influenced attitudes. Close and open communication was seen as a facilitator of FH discussions, whereas a family culture that did not include medical conversations was seen as a barrier. Several participants cited challenges in convincing their young adult children to be tested, noting that logistical barriers, lack of interest and competing priorities, and mixed messages from medical providers about the significance of high cholesterol in early adulthood served as barriers. Participants described several factors that would facilitate screening, including offering written materials to help them explain FH to family members and ensuring easy testing and follow up for those who agreed to screening, with a particular focus on minimizing the number of appointments and health care contacts required to

complete the screening process. Other recommendations included being specific about which family members should be screened and being sensitive to the fact that some family members may live far away or not have easy access to care. Many individuals were open to the idea of their relatives being contacted directly by a medical provider or other person knowledgeable about FH, but they saw both opportunities and challenges with this approach; recommendations included ensuring clear communication about why the relative is being contacted, what their risk is, how important it is to be screened, and offering convenient screening options (e.g., multiple lab locations, in-home testing, telehealth). Several people mentioned that unsolicited outreach might be perceived as spam unless probands gave advance notice of the contact. Others preferred to contact relatives themselves. Patients also noted that some family members might be hesitant to engage in screening due to lack of trust in the medical system or concerns about having their information shared.

Clinician Themes

Themes identified in clinician interviews included perceptions of the value of FH screening and diagnosis, current FH-related practice and context, and attitudes toward centralized tools to aid clinical practice. Sample quotes from clinicians are included in Table 2.

Perceived value of FH screening and diagnosis

Participating clinicians had varying attitudes about the value of FH screening and diagnosis and whether it provided actionable information. Attitudes were typically connected to the degree of accuracy of their knowledge of FH and how it should impact clinical care. Several clinicians believed that knowing FH status would not result in any difference in treatment, whereas others characterized it as very important for identifying an appropriate treatment plan and notifying family. Some felt awareness of FH status and family history helped motivate patients to engage in preventive care.

Current FH-related practice and context

Clinicians varied in their self-reported degree of familiarity and comfort in identifying and treating FH. They echoed patients who highlighted logistical barriers, such as limited appointment availability. Clinicians also discussed the challenges of caring for complex patients with multiple comorbidities and noted that a condition like FH was sometimes difficult to prioritize. Several participant comments reflected a perception that FH is not as life-threatening as genetically linked cancers might be. Multiple participants also noted the difficulty of addressing specific issues within very large patient panels and feeling generally overwhelmed with the responsibilities of needing to address more and more issues within primary care.

Attitudes toward centralized tools

Some clinicians thought adequate screening was already occurring and thus did not see the value in a screening tool such as FIND FH or increased screening in general. Others thought that the FIND FH tool could be useful in prompting conversations, especially if the tool was based on published research and had balanced sensitivity and specificity. Several clinicians emphasized the need for centralized tools to be integrated carefully into clinical practice and expressed dislike of additional alerts that can interrupt workflow (e.g., by requiring documentation to proceed, by going off while they were completing a different task) and of decision support tools that were lengthy. Regarding cascade screening, clinicians acknowledged time and capacity limitations in their ability to drive this process and noted that having written or digital materials to share with patients would be helpful, while also noting variable communication preferences among their patient populations. Some clinicians also expressed a belief that communication with family members should come from patients, rather than the patient's clinician.

Discussion

This qualitative investigation of patient and clinician perspectives on the use of EBPs along the FH care pathway in the U.S. identified patient and clinician confusion about FH and its unique treatment needs, lack of urgency around identification and treatment of FH, and lack of time and competing priorities as common implementation barriers. Patient interviews also captured FH's emotional impact on individuals and families, concerns about conflicting information from clinicians, and barriers to accessing care. Variable accuracy of FH knowledge and parallel concerns about health care access barriers were present in clinician interviews.

Overall, these findings are consistent with other investigations of barriers to FH diagnosis and treatment [14–17, 19–21] and support the potential value of behavioral economics-informed implementation strategies to improve adherence to EBPs along the FH care pathway. The prevalence of misconceptions and knowledge barriers about FH and its treatment suggest that concise, easy-to-understand, "off the shelf" solutions may be needed to reduce ambiguity about best practices and create a shared language, both between patients and clinicians and between primary care providers and FH specialists. To increase the likelihood that improved knowledge will translate into action, application of the EAST framework from behavioral economics—which emphasizes

Table 2 Selected Clinician Quotes

Themes	Quotes
Perceived Value of Knowing FH Status	
	Yeah. I don't feel like it's particularly useful, other than the family history and potentially ramifications for their family. (1091)
	I guess the importance is in motivation for the patients… often I find my patients are motivated by family events. And so, although I am often having the conversations of statins can prevent heart attacks and strokes, I think if you're able to tie it to, this runs in your family. Here are these negative consequences. This is why you are, specifically, at higher risk. This is why diet and exercise will not work for you. That is where I find it's probably most important to help with the initiation and adherence to these medications. (1078)
	I think they would want to know what they can do about it to fix it. […] I think telling them that it's a treatable condition that might have a very – an impact on their life expectancy and health status. (1081)
	I think that if I had a clearer sense that having this specific diagnosis attached to the patient, that a patient sort of being diagnosed with FH would garner the patient any additional resource or treatment that was specific to FH beyond just risk prevention and cholesterol management. Probably if I knew that information, it's probably out there. I don't know it. And so knowing that information would probably help. (1103)
Current FH Practices	
	…I don't know if I'd give it any more weight than other causes of high cholesterol. If there is – if I'm really suspicious of it – so if someone's LDL is greater than 200 […] Or if they're young, and their LDL is 180 plus, and they have a significant history of family heart disease […] then I get more concerned. But – and then in that case, I might do a statin plus a referral to preventive cardiology or something. (1005)
Patient-level barriers	
	It usually tends to be just the overall complexity of their chronic conditions. So, these are patients that aren't just dealing with this one diagnosis. But they have a lot of other comorbidities that require medications. And I would say one of the major barriers is just prioritization. A second barrier is that this is all prevention, usually. And so, trying to have a patient understand their risk and taking a medication to lower their risk, is kind of an abstract concept. And oftentimes, patients aren't at the point where they feel at risk. And therefore, they don't feel like they should have to take a medicine. (1091)
	Well, I mean, my patient population is, again, urban Philadelphia so there's a lot of distrust of healthcare and the systems in general, so I think that's just a general issue with any kind of medical intervention. But I also think that counseling and information and education addresses that barrier, usually. (1081)
Practice-level barriers	
	And I think that we're just asking more and more of our providers – and we don't give them any time to do this. And we don't take away any tasks. We're adding. We are never removing a BPA [best practice alert]. We are only adding…I think we need to have – give our PCPs probably more time with smaller panels so that we can engage in all of this good, high-quality care. And that's just going to take time as we move in our value contracts. There's no quick answer for this." (1078)
	I think, generally, people would be open to [family screening]. I think probably we under – I would say that I might underemphasize that […] I think there are some things, like breast cancer, et cetera – that it's very hardwired and you would never not think about it. But I just – in reflecting, I now have to go back and think, do I always emphasize it? (1078)
Attitudes Toward Centralized Tools to Aid Clinical Practice	
	With any clinical decision-making tool, it just depends how easily it kind of can be used within your standard workflow. I think if it's something where I have to go somewhere separately to access to it and/or review it, it could be challenging. (1009)
	I think a tool like this should be done in the background, and not as a pop up. And I think if the tool could be done, and then the provider could get a letter about, this person is at risk for FH, this would be the recommendation, I think that would be helpful. Again, but nothing that I would have to opt in for, I think would be important. But no pop ups, please. (1086)
	I think the other thing is with FH I would assume that there's no immediate urgency, in the sense that it is important to know, but you could go a couple of years without knowing. And thus if a flag were to come across my screen saying, consider FH, I would say, here's something you should think about, take some time to think about it, if you want to we'll run the test, it's okay. It's very different than saying, this person probably has lung cancer across your screen and feeling like this, I need to do something immediately, drop everything you're doing. (1095)
	When we see a BRCA family, we're not calling all their relatives. We're not their doctors. We are asking them to do it. But it sure would help if we had something easy available to guide that discussion or something, because usually it's probably a pretty weak intervention […] I think the alternatives are tough, because just calling patients who aren't enrolled as our patients is a tough issue. (1125)
	I think if they had some sort of handout or something they could share with their family members, it would make it easier. I think most of my patients fall into two general groups in terms of their familiarity with IT and existing devices, so half of my patients probably would be, you know what I mean, more likely to have something on their iPhone that they could forward, text to their family members or email. And half actually would prefer some other – a handout. (1081)
	I think tasking the patient with conveying this to other family members and maybe giving them some sort of a resource to use, so that they don't have to feel like they need to remember everything that I said. (1158)

the importance of making decision pathways easy, attractive, social, and timely [50]—suggests the need to draw direct links between information and action steps and to emphasize available resources, in order to simplify decision-making and boost follow-through. Indeed, participating patients who were able to articulate how their FH diagnosis impacted their treatment plan noted that this had affected their treatment engagement (e.g., increasing acceptance of the need for medication and commitment to long-term adherence) and participating clinicians with more accurate FH knowledge reported greater investment in FH care. This highlights the potential for action-oriented education to facilitate engagement with FH-related EBPs.

Specifically, the knowledge deficits we observed suggest that patient- and clinician-facing education should focus on (a) why screening for FH is valuable (e.g., actively addressing the misconception that all high cholesterol is the same), (b) how an FH diagnosis should influence treatment plans (e.g., universal need for pharmacological treatment, need for earlier and more intensive treatment), (c) that undiagnosed and untreated or under-treated FH is a time-sensitive issue even in people perceived to be "young and healthy" (e.g., atherosclerosis begins in childhood, early treatment can dramatically reduce risk of early cardiovascular events and death), and (d) that clarifying one's FH status can have emotional benefits (e.g., avoiding regret and disappointment when lifestyle changes are insufficient to bring LDL-C to safer levels, reducing worry, protecting loved ones). Clear instructions on what to do when FH is suspected or diagnosed (e.g., how to get screened, how to find care, how to pursue family screening) are also critical. Drawing on additional behavioral economics concepts, messaging may be most successful when it references social norms, minimizes response burden (e.g., providing universal education rather than requiring people to sign up or opt in), balances risk-framed and gain-framed messaging, and incorporates deadlines to nudge task completion. Our findings also highlighted the importance of incorporating principles from behavioral medicine [51], such as attending to the emotional impact of health issues in a family; emphasizing the emotional benefits of taking action; naming and normalizing common concerns; and accommodating diverse needs, preferences, and family cultures whenever possible (e.g., offering multiple pathways for contacting relatives for family screening).

Our findings also suggest that shifting primary responsibility for FH identification toward more centralized implementation strategies, such as direct outreach to patients and families via a centralized program or "hub," may increase efficiency and aid early diagnosis and treatment of FH. Centralized delivery of educational messaging and expert consultation—such as via direct outreach to patients outside of clinical visits—may be especially useful for FH. FH is potentially life-threatening, but our findings reflect that its initial presentation (high cholesterol) is often considered a routine health issue by both patients and clinicians, even when clinicians are knowledgeable about FH. Because FH is likely to be responsible for a very small percentage of the cases of high cholesterol in an individual primary care clinician's patient caseload, centralizing outreach efforts can address cognitive biases that may inhibit accurate detection and diagnosis in routine care. For example, clinical decision-making ideally incorporates base rate data; medical education frequently teaches clinicians to "think horses, not zebras." Due to the high prevalence of lifestyle-mediated high cholesterol in adults and the relatively low prevalence of high cholesterol in young people, this creates a bias toward routine cholesterol management practices (e.g., lifestyle changes as an initial treatment choice, low urgency in younger patients). Thus, centralized implementation programs that flag and follow up on patients at high risk of FH, communicate directly with patients, and coordinate with primary care may be more efficient than changing individual clinician mindset and behavior. This is likely to be especially true for improving diagnosis in children given that both clinicians and parents may not be conditioned to proactively raise concerns even in at-risk children. Although pediatric practice guidelines recommend routine cholesterol screening that could flag FH risk, one large national claims-based analysis found that only 20% of standard-risk youth and 47% of high-risk youth (i.e., with a medical diagnosis conferring higher risk) were screened [52]. Centralized efforts have been successful in several countries (e.g., the Netherlands [53, 54]) but have been difficult to replicate in the U.S. due to challenges including population size and lack of a universal health care system. Concentrating and tailoring these efforts within individual health systems may mitigate these barriers.

Implementation science frameworks emphasize the importance of aligning change efforts with constituent perspectives [55–57]. In light of clinician feedback that competing demands inhibit detection and management of FH, framing new centralized tools and programs as an opportunity to increase accurate diagnosis and optimal care while reducing clinician burden may be useful. Our patient participants were generally enthusiastic about the prospect of centralized efforts. From a behavioral economics perspective, centralized programs that include elements that reduce "sludge" (barriers) and make it easier to engage in recommended behaviors [58] are also likely to increase buy-in. Based on our findings, this might include free screening offered through labs with national reach, free consultation with FH experts offered through health systems or in collaboration with nonprofit organizations such as the Family Heart Foundation, and telehealth options.

Finally, the fact that our study focused on patients who had already participated in a quality improvement program designed to detect undiagnosed cases of FH resulted in several additional insights for implementation strategy design. Many individuals did not remember details of their program participation (which was 3–4 years prior) and were uncertain about whether they had FH and/or how FH was unique. The prevalence of this confusion suggests that many individuals are likely to need repeated exposure to FH-related health messaging

that is easy to understand and remember. Prior research has shown that written materials can aid patient recall [59–61], and giving patients materials that are designed to be shared with their personal clinicians would serve the additional purpose of addressing knowledge gaps among primary care clinicians and gaps in care coordination. This could decrease the likelihood that conflicting information about best practices for FH-related high cholesterol will be communicated to patients. Our findings also suggest that individuals with FH who are contacted about family screening efforts months or years after their FH diagnosis may need reminders about their own diagnosis and its implications, clear messaging about how family screening can benefit relatives, and assistance delivering key information to family members.

Our study's goals and design have implications for its generalizability and the transferability of findings [62]. We focused on patients and clinicians sampled from one health system, and all patients had participated in a prior FH-related study; their impressions and experiences may differ from individuals in other health care settings or regions, and patient perspectives may not represent individuals who have had no health care contacts related to FH. Our clinician sample was restricted to physicians and may not reflect the experiences of advanced practice providers. In addition, our patient sample had limited racial and ethnic diversity. This may reflect the fact that FH is underdiagnosed in Black and Asian communities in the U.S. but is an important limitation because individuals who *are* diagnosed in these communities have also been found to be treated later and/or less effectively compared to white individuals. Efforts to ensure equity in implementation of FH-related EBPs are especially critical given that individuals from racially and ethnically minoritized groups also experience inequities in treatment of cardiovascular risk factors such as hypertension and diabetes, which may exacerbate the negative health outcomes of delayed FH diagnosis. It is also important to note that a recent meta-analysis found that FH prevalence data are available for only 17 countries worldwide [3]; from a global perspective, there is still much to be learned about how to improve diagnosis and optimal treatment across diverse populations and health care settings. Nonetheless, many of our core findings (e.g., the need to address knowledge deficits) are likely to be important across populations, settings, and countries.

Conclusion

The constituent input reported here exemplifies the importance of centering patient and clinician experiences in efforts to improve routine care. This feedback has been invaluable for implementation strategy and trial design for our hybrid effectiveness-implementation trials of behavioral economics-informed patient- and clinician-focused strategies to increase evidence-based care for FH within a large health system (implementing the FIND FH tool, MPIs Volpp and Rader, W81XWH2110421; and employing patient-facing strategies to promote family screening for FH, MPIs Beidas, Volpp, and Rader, R33HL161752). Study insights may also benefit other future implementation studies addressing FH or other genetic conditions.

Abbreviations

U.S.	United States
FH	Familial hypercholesterolemia
LDL-C	Low-density lipoprotein cholesterol
ASCVD	Atherosclerotic cardiovascular disease
EBP	Evidence-based practice
EHR	Electronic health record

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Authors' contributions

ARP contributed to analysis and interpretation of patient and clinician data, drafted major portions of the manuscript, and revised the manuscript. TK led interview guide development and analysis and interpretation of the patient and clinician data and revised the manuscript. RCK analyzed and interpreted patient and clinician data, drafted the manuscript, and revised the manuscript. CJ contributed to interpretation of data, drafted portions of the manuscript, and revised the manuscript. NO contributed to interpretation of data and revision of the manuscript. MM led acquisition of patient and clinician data. KS and JS contributed to acquisition and analysis of patient and clinician data. LN and JAO contributed to conception and design of the study. AL contributed to conception and design of the study and data acquisition. MPM contributed to conception and design of the study and revision of the manuscript. ET contributed to interpretation of data. JC contributed to conception and design of the study. DJR, KGV, and RSB led conception and design of the study, secured funding, contributed to interpretation of data, and revised the manuscript. All authors read and approved the final manuscript.

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Data availability

Data are not publicly available because participant privacy could be compromised.

Declarations

Ethics approval and consent to participate

This study was approved by the University of Pennsylvania Institutional Review Board (Protocol #849516). Informed consent was obtained from all participants.

Consent for publication

Not applicable.

Competing interests

At the time of the study, MPM was Chief Medical Officer at the nonprofit Family Heart Foundation. ET is a genetic counselor and care navigator at the Family Heart Foundation. DJR is the Chief Scientific Advisor and immediate

past Chair of the Board at the Family Heart Foundation and is on the Scientific Advisory Board of Alnylam Pharmaceuticals, Novartis, and Verve Therapeutics. He is a founder of VascularStrategies LLC and a consultant for Regeneron Pharmaceuticals, Inc. KGV is a part-owner of VALHealth, a behavioral economics consulting firm, and receives research funding from Independence Blue Cross and research funding and consulting support from the American Heart Association, none of which are related to the work described in this manuscript. He is also a Scientific Advisory Board member of Thrive Global and receives equity stock options for his role (also unrelated to this manuscript). RSB is the principal at Implementation Science & Practice, LLC. She receives royalties from Oxford University Press and consulting fees from United Behavioral Health and OptumLabs. She is currently an appointed member of the National Advisory Mental Health Council and the NASEM study, "Blueprint for a National Prevention Infrastructure for Behavioral Health Disorders," and serves on the advisory boards for AIM Youth Mental Health Foundation and the Klingenstein Third Generation Foundation, outside of the submitted work. The remaining authors (ARP, TK, RCK, CJ, NO, MM, KS, JS, LN, JAO, AL, and JC) declare that they have no competing interests.

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