Assessing Pediatric Provider Attitudes Regarding the Diagnosis and Management of Familial Hypercholesterolemia

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Familial hypercholesterolemia (FH) is a common autosomal dominant inherited disorder which greatly increases a person's risk for cardiovascular disease and premature mortality. Current guidelines from the National Heart Lung and Blood Institute (NHLBI) recommend universal pediatric screening for FH, but the actual screening rate is only about 20%. The underdiagnosis of FH is recognized as an urgent public health problem. FH has been named a CDC Tier 1 Genomics Application condition and is easily diagnosed through lipid panel screening and genetic testing. Adverse health effects of FH can be managed with early medical intervention, but it is often not diagnosed until after a serious cardiac event. Early identification of FH also provides an opportunity for cascade screening which benefits family members with pre-clinical FH. This paper seeks to elucidate potential reasons for low screening adherence in the context of pediatric provider attitudes toward and understanding of FH.

Provider attitudes were assessed in the context of a Continuing Education and Quality Improvement (CEQI) project entitled "Addressing Familial Hypercholesterolemia" which was offered at no cost to participants. Of the 278 participants (N = 279) who registered for the training, 27 participants (9.7%) completed Pre- and Post-Knowledge Assessments and provided qualitative feedback on their perceptions of FH, the efficacy and feasibility of universal lipid screening, and planned changes to their clinical practice based on the knowledge gained.

Results showed that prior to the educational program, providers had poor knowledge of FH as a disease and of the reasoning why universal pediatric screening for FH is important. Participants also reported low confidence in managing FH in their patients, which was also attributed by some to be based in a lack of knowledge. However, upon completion of the training, all participants reported increased knowledge and confidence about FH screening and management, with the average ratings for each category increasing between 39.7%-52.9%. Furthermore, chart audit data showed that 73.0% of the participants' patients seen after participation had lipid panels ordered to screen for FH. These preliminary findings demonstrate that increasing knowledge and awareness of FH may ameliorate underdiagnosis of FH and poor adherence to screening guidelines.

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Preface

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1.0 Introduction and Background

Familial hypercholesterolemia (FH) is an inherited genetic condition which causes elevated low-density lipoprotein (LDL) cholesterol levels beginning in childhood. FH is included in the Centers for Disease Control and Prevention (CDC) Tier 1 Genomics Applications. This indicates a high level of evidence for significant positive impacts for public health from the diagnosis of FH.[1] The inheritance pattern of FH is autosomal dominant. There are two forms of FH: heterozygous FH (HeFH) and homozygous FH (HoFH). The homozygous form of the disease has a far more severe phenotype than the heterozygous form. Both forms of the disease yield increased LDL cholesterol levels in childhood, but in HoFH, the risk for cardiac events and heart disease is much higher at a much earlier age.[2] FH is a common disease, with a prevalence of approximately 1 in 250 people, most of whom are undiagnosed.[1,3] Notably, approximately 40% of patients who are diagnosed with FH worldwide do not have an identifiable pathogenic variant in one of the genes associated with FH. These patients are diagnosed with "clinical" FH based on diagnostic guidelines set forth by various professional organizations.[4–6] FH affects people worldwide, and improvement of FH diagnosis and screening is a priority in many countries.[7,8]

Multiple health agencies and organizations – including the Family Heart Foundation (FH Foundation), American Heart Association (AHA), National Lipid Association (NLA), and National Heart, Lung, and Blood Institute (NHLBI) – recommend that all children between the ages of 9 and 11 should receive a lipid profile screening. For those with a family history indicative of FH, it is recommended to screen children beginning at age 2.[9,10] These screenings identify children with abnormally high lipid levels who can then be referred for genetic and diagnostic testing for FH and other conditions. Pediatric lipid screenings for FH are important, as there are

effective interventions for FH which can greatly reduce the risk of atherosclerotic heart disease and cardiac events as well as improve the quality of life for affected individuals.[10,11] Identification of FH in a patient can also have positive impacts on the health of their family members, as reverse cascade screening can lead to early intervention for children's parents and siblings.[12] However, there is currently poor adherence to these screening guidelines, with a national baseline of only 20%.[13–16] This poor adherence has been attributed to poor knowledge among healthcare providers about FH and lack of awareness of pediatric lipid screening guidelines, but there is little research into the reasons underlying low screening rates.

This thesis project is a collaboration with the Michigan Public Health Institute (MPHI) for the evaluation of a Continuing Education and Quality Improvement (CEQI) program titled "Addressing Familial Hypercholesterolemia" which was implemented by their Center for Strategic Health Partnerships (CSHP). The goal of this project is to have providers participating in the program implement universal lipid screening for children ages 9-11 following CEQI program completion to increase rates of diagnosis and early intervention for FH.

The CEQI training survey responses will be systematically analyzed, with a focus on the attitudes of clinicians towards lipid screening in children. Qualitative data analysis is used to investigate patterns of understanding of current screening recommendations, knowledge of the implications of undiagnosed FH for future health outcomes, and attitudes toward treatment of FH in pediatric populations. After codifying these results, trends in responses are reported and interpreted to recommend changes to the CEQI program for future participants. These recommendations have the goal of increasing clinician comfortability with FH diagnosis and management. The primary stakeholders for this project are physicians who participate in the CEQI program. Secondary stakeholders include patients who qualify for lipid panel and FH screening.

Both populations would benefit from healthcare providers with better understandings of the importance of lipid screening in pediatric populations and who are less averse to the treatments for children with homozygous or heterozygous FH.

Specific Aims:

1. Utilize data from post-quality improvement training surveys to assess pediatric provider attitudes and areas of discomfort regarding the diagnosis and management of FH in children.
2. Examine bioethical implications of published lipid screening guidelines, especially concerning the "prevention paradox" and the tension between principles of autonomy and beneficence.
3. Synthesize ethical considerations together with analysis of provider attitudes in the setting of the CEQI project to make general recommendations for future directions regarding professional educational programs about the practice of screening, diagnosis, and management of FH in pediatric populations.

1.1 Phenotype and Clinical Indications of Familial Hypercholesterolemia

FH is an autosomal dominantly inherited condition characterized primarily by elevated LDL serum levels beginning in childhood, regardless of diet or lifestyle factors. FH is associated with accelerated development of atherosclerotic plaques in coronary arteries and earlier onset of adverse cardiac events in affected patients.[2,17–19] This increased risk is attributed to lifelong exposure to elevated LDL cholesterol. Although this has not been extensively studied specifically in the context of FH, it is well known that increased duration of elevated lipids is associated with

higher risk for cardiac disease and cardiac event mortality.[8,17,19] Some unique phenotypic features seen in severe cases of FH include tendon xanthomas, which are accumulations of lipids visible beneath the skin, and cornea arcus, which is the development of a silver-white ring around the patients' cornea resulting from excess lipids stored in corneal tissues.[20,21]

The estimated prevalence of FH varies due to the pervasive issue of underdiagnosis. As screening programs become more widely implemented, the estimated prevalence of FH has increased.[2,22] It is currently estimated that the heterozygous form of FH affects between 1 in 200 to 1 in 300 people. The homozygous form of FH has historically been estimated to affect 1 in 1,000,000 people, but recent consensus has postulated that the true prevalence is closer to 1 in 160,000.[2,23,24]

1.2 Genetic Background of FH

FH has two main forms: heterozygous FH (HeFH) and homozygous FH (HoFH). HeFH results from the presence of a pathogenic variant in one allele of an associated gene, and HoFH results from a pathogenic variant in two alleles. HoFH can be biallelic, a true homozygous form, where there are two pathogenic alleles in the same gene which contribute to FH. HoFH can also result from compound heterozygosity, where the affected patient has two different pathogenic alleles in the same gene or in two different genes.[2,23] There are four known genes associated with the development of FH: *LDLR, APOB, PCKS9*, and *LDLRAP1*.

1.2.1 *LDLR*

The most common genetic cause for FH is a loss of function mutation in the *LDLR* gene, which accounts for between 70-80% of FH cases. The *LDLR* gene encodes LDL receptor proteins, and different variants result in different mechanisms for a loss of function. For example, some variants may be receptor-deficient and result in reduced ligand-binding through reduced binding affinity or decreased expression of LDLRs on the cell surface. Other variants may result in the complete lack of the LDL receptor and are referred to as receptor-negative variants.[23]

1.2.2 *APOB*

The second most common is a loss of function mutation in the *APOB* gene, which accounts for about 2-5% of cases. Variants in this gene are inherited in an autosomal dominant pattern, although different variants in the *APOB* gene may have varying levels of penetrance.[23,24] Some known variants in the *APOB* gene are also more commonly seen in different ethnic populations. Specifically, the variant Arg3500Gln is most common in Northern European populations, while Arg3500Trp is more common in Chinese populations.[23]

1.2.3 *PCSK9*

The third gene associated with FH is the *PCKS9* gene. The molecular mechanism of this form of FH is a gain of function mutation that results in the degradation of LDL receptor (LDLR) proteins. This form of FH is rare, affecting less than 1% of patients with FH, but has a severe phenotype. However, this mechanism makes the *PCKS9* gene an ideal target for gene therapy

treatments for FH because the inhibition of the *PCKS9* gene will result in the reduction of LDL serum levels (regardless of which form of FH has been inherited).[24]

1.2.4 *LDLRAP1*

A rare autosomal recessive form of FH occurs due to a loss of function in the *LDLRAP1* gene. This gene encodes a protein which is crucial for the internalization of LDL receptors in liver tissue. The loss of function in the LDLRAP1 gene impairs the cell's clustering ability for clathrin-mediated endocytosis, which in turn results in higher levels of LDL-C in the bloodstream.[2,23,24] This form of FH is most common in Sardinian, Lebanese, Ashkenazi Jewish, and consanguineous populations.[23,24] Information on the prevalence and functional consequences of variants in the genes associated with FH is summarized below in Table 1.

Table 1: Summary of Genetic Information for Familial Hypercholesterolemia (FH)

Gene	Inheritance Pattern	Loss of Function (LoF) or Gain of Function (GoF)	Pathophysiology	Proportion of Cases
LDLR[3,23]	Autosomal Dominant	LoF	LDLRs not synthesized, not properly transported to cell surface, or not recycled back to cell surface	70-80%
APOB[23,24]	Autosomal Dominant	LoF	Reduced affinity of LDLR binding site	5-10%
PCSK9 [2,9,24]	Autosomal Dominant	GoF	Increased PCSK9 proteases leads to increased degradation of LDLRs	<1%
LDLRAP1 [2, 23,24]	Autosomal Recessive	LoF	Impaired clustering for clathrin-mediated endocytosis of LDL-LDLR complex	<1%

1.3 Diagnosis of FH

There are several widely accepted diagnostic guidelines used for the diagnosis of FH. The first set of diagnostic guidelines for FH to achieve widespread acceptance is the Dutch Lipid Clinic Network (DCLN) Score. DLCN guidelines are based on a point system, where scores less than 3 indicate unlikely FH, 3-5 indicate possible FH, 6-8 indicate probable FH, and scores over 8 indicate definite FH.[25] Points are given based on indications regarding:

- family history of premature cardiovascular disease, hyperlipidemia, or physical symptoms like tendon xanthomas or arcus cornealis,
- patient presentation with premature cardiovascular, cerebral, or peripheral vascular disease, tendon xanthomas, arcus cornealis before age 45, elevated LDL-C, and
- presence of a pathogenic variant in functional analysis of *LDLR, APOB,* or *PCSK9*.[23,25,26]

Criteria are weighted from anywhere between 1-8 points. One benefit of the DLCN criteria is that the genetic analysis component allows for identification of the specific molecular defect which underlies the pathophysiology of the patient's form of FH. This allows for a more targeted strategy for the management of the condition.[20,25]

Another well-known set of diagnostic guidelines for FH is the Simon-Broom criteria. The Simon-Broome criteria, like the DLCN score, uses both genetic and clinical indications to diagnose FH. Under these criteria, a diagnosis of definite FH requires total cholesterol levels greater than 290 total cholesterol mg/dL total cholesterol (190 mg/dL LDL-C) for adults, or 260mg/dL total cholesterol (155 mg/dL LDL-C) in children, as well as either the presence of tendon xanthomas in the patient or a first- or second-degree relative, or a positive genetic test for a pathogenic variant in one of the genes associated with FH. A diagnosis of possible FH could be given in cases where

there is history of premature cardiac events (under age 60 for first-degree relatives and under age 55 for second-degree relatives) or history of hyperlipidemia (greater than 290 mg/dL) in first- or second-degree relatives.[25,27,28]

In the United States, another set of diagnostic guidelines called Make Early Diagnosis to Prevent Early Death (MEDPED) is used for FH diagnosis. The MEDPED diagnostic criteria is a series of LDL-C level cutoff points based on age and degree of relation to a family member with an FH diagnosis (see Appendix A). Drawbacks of the MEDPED criteria are the lack of clinical indications used to aid diagnosis and the lack of consideration of genetic factors.[23,25] However, there is also a benefit to the MEDPED criteria not including genetic factors, as a large proportion of patients with clinical diagnoses of FH do not have an identifiable genetic cause for their FH. Nevertheless, genetic testing can help inform a diagnosis of FH regardless of the set of diagnostic guidelines used. A positive genetic test showing a pathogenic variant for FH can confirm a diagnosis of FH. However, a negative or uncertain result does not exclude FH, as there may be other genetic variants or polygenic effects that result in FH.[9,17,24,26,29,30] See Appendix A for a summary of current diagnostic guidelines for FH.

Recently, there has been some criticism of the currently widely accepted diagnostic criteria, with expert panels claiming that DCLN criteria are not appropriate for pediatric diagnosis.[31] Other critics have said that the requirement of DCLN and Simon-Broome criteria on confirmation genetic testing limits diagnosis because currently around 40% of patients with FH do not have an identifiable pathogenic mutation.[32–34] Based on these perceived deficits, the European Atherosclerosis Society (EAS) published recommendations for diagnostic guidelines that acknowledge a positive genetic test as an ideal method of diagnosis, but an LDL-C level of 135mg/dL or greater in a child with a known family history of FH is sufficient for diagnosis.

According to EAS guidelines, in children with no family history of FH, a clinical diagnosis may be made if total LDL-C levels are elevated at or above 135mg/dL in two successive lipid profiles given at an interval of 2-3 months or if they have a parent with a DCLN score greater than 5.[31]

1.4 Treatment for Pediatric FH Patients

Treatment should be initiated immediately following a diagnosis of FH. There are many safe and effective treatments available for pediatric patients identified with FH. The standard treatment goal for pediatric patients with FH is 130mg/dL total LDL or a 50% reduction in initial LDL levels.[9,20,35] Statin drugs are the primary means of treatment for FH. Recommendations hold that statin drug treatment be initiated as soon as possible for all patients with FH.[19,21,27] Currently in the United States, pravastatin is approved beginning at age 8, and all other statin drugs are approved for use at age 10.[10,19] Statins decrease LDL-C levels through the inhibition of the 3-hydroxy 3-methylglutaryl-CoA (HMG-CoA) reductase enzyme, which interrupts the metabolic pathways for cholesterol synthesis and upregulates the synthesis of LDLRs.[19] Despite demonstrated safety and efficacy of statin use in pediatric patients, there remains hesitancy from healthcare providers to prescribe statins to children, even in the setting of an FH diagnosis.[36,37] Most practitioners prescribe diet and lifestyle changes as the primary strategy to manage FH, even in the case of HoFH.[36–38] While diet and lifestyle factors are important components of managing FH, they are demonstrably insufficient to manage the condition.[19–21]

There are several other treatments that are used in combination with statins in cases of statin resistance or to manage LDL-C levels when statins alone cannot meet target LDL levels. Ezetimibe is a drug which inhibits absorption of LDL-C in the small intestine and can yield a 15-

20% reduction in LDL-C levels. Ezetimibe is generally well-tolerated in patients and is approved for use beginning at age 10.[26] Bile acid sequestrants may also be used in combination with other treatments to achieve additional lowering of LDL-C, but often have significant gastrointestinal side effects that lead to poor treatment adherence. These drugs work by binding bile acids in the liver to competitively inhibit the reabsorption of LDL-C.[19,26,39] Niacin is also frequently used in conjunction with other pharmacological treatments to bring down LDL-C levels. Niacin helps to both lower LDL-C and increase high-density lipoprotein (HDL), which has a protective effect on cardiovascular health.[19,26,37,40]

PCSK9 inhibitors are an emerging pharmacological treatment for FH that use monoclonal antibodies designed against PCSK9 proteins. These antibodies inhibit the function of PCSK9 proteins to prevent the degradation of LDLRs and can be useful in cases of FH from multiple variants.[11,38] However, to be effective there must be some residual function of LDLRs in the patient's hepatocytes, as PCSK9 inhibitors do not upregulate the expression of the receptors, but simply prevent their degradation. PCSK9 inhibitors are approved for use in children 10 years and older.[11,19,41]

When pharmacologic treatments are ineffective or unavailable, lipid apheresis is used to remove LDL-C from the bloodstream. Lipid apheresis involves the active removal of LDL-C from circulation using plasmapheresis technology. This process occurs every 1-2 weeks and must be performed in a specialty clinic.[27,42] Lipid apheresis is costly and often difficult to access, which can be a significant barrier to treatment. Lipid apheresis is safe to be used in children as young as 3 years of age, making it one of the earliest possible interventions for FH. This is especially important when considering the treatment of HoFH, which has a severe, early onset which can lead to adverse cardiac events in the first decade of life. As most FH treatments are not approved

for use until children are at least 10, lipid apheresis provides a critically needed treatment for these patients.[20,30,42] For patients with HoFH, it is recommended that lipid apheresis begin prior to 6-7 years of age to prevent pathogenic effects on aortic root formation.[42,43]

While not yet approved for pediatric patient use, there are some experimental gene therapy technologies which use antisense oligonucleotides to interfere with messenger RNA of *APOB* to reduce the amount of LDL in circulation. One such treatment, called mipomersen, has been tested in pediatric patients aged 12 years old or more and has yielded a reduction of LDL-C of over 25% in cases of HoFH and severe HeFH.[19]

As alluded to above, the course of treatment for HeFH and HoFH are generally quite different, especially among pediatric populations. Children diagnosed with HoFH require immediate, aggressive treatment from the time of diagnosis. This course of treatment is recommended to include high-dose, high-intensity statins used in combination with ezetimibe and lipid apheresis.[17,19,44] For children diagnosed with HeFH, a low-dose, low-intensity statin should be started at time of diagnosis and increased as needed to meet LDL-C goals.[19,26,30] The described treatment options for FH are summarized in Table 2 below.

Table 2: Summary of Current Treatment Options for FH

Treatment	Mechanism of Action	Age Approved for Use (years)	Relative Cost	Side Effects
Lifestyle/diet changes[36–38]	Limitation of exogenous cholesterol, physical activity to reduce LDL-C levels	All ages	Low	Social barriers/stigma
Statin drugs[9,19,27]	Inhibition of HMG-CoA and increased LDLR expression	Pravastatin – 8 & up All others– 10 & up	Low	Myalgia, myopathy
PCSK9 inhibitors[11,38,45,46]	Monoclonal antibody binds to PCSK9 enzyme to inhibit degradation of LDLRs	10 & up	High	Myalgia, influenza-like symptoms, immunodeficiency
Ezetimibe[17,26,44]	Prevention of LDL-C absorption in small intestine	10 & up	Moderate	Headaches, gastrointestinal symptoms
Bile acid sequestrants[19,26,39]	Binding of LDL-C to	10 & up	Moderate	Gastrointestinal symptoms; vitamin deficiencies
Niacin[19,26,37,40]	Inhibition HDL-C catabolism and decreased secretion of LDL-C	All ages	Low	Nausea, elevation of liver transaminases, hyperglycemia, hyperuricemia
Lipid apheresis[19,20,30,42]	Extracorporeal removal of LDL-C by plasmapheresis	3 & up	High	Hypotension, anemia, tendency for bleeding, immunocompromised

1.5 FH Screening Strategies and Recommendations

FH poses a significant public health burden both in the United States and abroad, and screening for FH is urgently needed. Many professional organizations and expert panels have released evidence-based statements on the need for FH screenings to reduce morbidity and mortality from premature cardiovascular disease,[7,8,20] though not all guidelines are supportive (See Table 3).[28] However, widespread systematic screening for FH has not been achieved in most countries, including the US.[7,8,14] Current guidelines from the NHLBI and AAP in the United States recommend universal screening for FH using non-fasting lipid panels and subsequent genetic

testing for children with elevated LDL-C levels at ages 9-11, and at age 2 for children with a family history of premature cardiovascular disease or death.[10] Some suggestions made by EAS are that repeat lipid panel testing after a period of three months for all patients between the ages of 2 and 10 may be more effective than current diagnostic criteria and screening recommendations.[31]

Table 3: Published Guidelines for FH Screening

Organization	Supports FH Screening?	If yes, type:
American Academy of Pediatrics (AAP)[10]	Yes	Universal, pediatric
National Heart, Lung, and Blood Institute (NHLBI)[10]	Yes	Universal, pediatric
World Health Organization (Representatives of the Global FH Community)[8]	Yes	Recommends screening be performed according to country-specific demands/abilities
US Preventative Services Task Force (USPSTF)[28]	No	n/a
Prague Declaration[7]	Yes	Universal, pediatric
European Atherosclerosis Society[31]	Yes	Universal lipid screening, pediatric, repeated after 3 months

The most commonly used strategy for FH screening is cascade screening.[5,33,47–49] Cascade screening refers to the practice of identifying one case of an inherited disease, called the index case, and subsequently testing their immediate relatives for the same disorder. As family members with the disorder are identified, their immediate relatives would be tested in turn. This method of screening for inherited diseases is widely employed across a range of genetic disorders. In the context of FH screening, a different form of cascade screening called "reverse cascade screening" has been suggested. This terminology helps differentiate FH screening strategies for adult and pediatric populations, which is important for early identification and intervention to prevent future atherosclerotic cardiovascular disease.[12] Reverse cascade screening is much the same as cascade

screening, but rather than testing children of affected parents, the child is the index case, and the parents would be tested next. This method is extremely suitable for FH detection given the FH is an autosomal dominant disorder, so if a child has a diagnosis of FH, at least one of their parents is most likely affected. Reverse cascade screening also has the benefit of early intervention, not only for the child, but potentially for their parents as well. Many parents with children aged 9-11 may not have experienced any outward physical symptoms of FH yet, so identification at the subclinical stage could help avert a premature cardiac event or death.[17,18]

1.5.1 Examples of FH Screening Programs

One of the most well-known screening programs for FH – the Dutch Lipid Clinic Network – was conducted in the Netherlands between 1995 and 2014. The program in the Netherlands was instrumental in the development of the DLCN Score guidelines for FH diagnosis. The DCLN also provided key evidence for the estimation of the true prevalence of FH (approximately 1:250 as opposed to the previously held estimation of 1:500). This state-funded program used an active cascade screening strategy where index cases were identified at adult specialty lipid clinics and nurses visited first-degree relatives at their homes to obtain informed consent for genetic testing.[22] The program in the Netherlands was extremely successful; however, when funding was discontinued screening and diagnosis rates for FH declined significantly.[5]

Two other long-standing FH screening programs were also established in Slovenia (est. 1995) and West Virginia (est. 1998). These screening programs are especially notable, as they are targeted at pediatric populations. The Coronary Artery Risk Detection in Appalachian Communities (CARDIAC) program in West Virginia is a universal screening program which screens fifth grade students for FH in combination with tests for hypertension, prediabetes, and

obesity, which contribute to cardiovascular disease and are all common comorbid conditions for FH.[50] While it is universal to the state of West Virginia, participation in the CARDIAC program follows the "OPT-IN" design and requires approval from the school district superintendent for school participation and parental consent for individual students. This program has been extremely successful at identifying families with FH, and multi-level interventions and support is given to participants and families.[50] The CARDIAC program also reports an estimated prevalence of 1:270 for FH, which aligns with current estimates. [50] In Slovenia, universal screening is done at age 5 during routine visits to their primary care physician. For this screening program, all children have total LDL-C levels tested and are referred for genetic testing for FH if their serum levels exceed 232 mg/dL or 193 mg/dL if there is a family history indicative of FH.[33] This screening program was gradually implemented, and the estimated detection rate for patients with FH increased from 53.6% in 2009 to 96.3% in 2013. Notably, despite children being 5 years old at the time of screening, the mean age for referral was 7.3, indicating a substantial lag in the time between testing, communication of results and initiation of treatment for FH. This may be an important indication of potential barriers to referral or initiation of treatment and underscores the need to screen patients at a young age to maximize the opportunity for early intervention.

Within the past ten years, there have been more concentrated efforts across the world to establish national FH registries. Examples of such registry programs include countries like Spain (SAFEHEART)[51], Germany (CaRe High),[49,52] Vietnam (VINAFH),[53] China (PEACE),[34] and South Africa (FIND-FH).[48] The strategies to identify patients with FH vary from country to country, but most use opportunistic screening methods followed by cascade screening. Due to the reliance of opportunistic screening on phenotypic symptoms such as extremely elevated LDL-C and experiences of early atherosclerotic cardiovascular disease or cardiac events, these registries

mostly identify adult patients with FH. As such, they also do not allow for early intervention except in the instance of the diagnosis of a child relative with FH through cascade screening.

In countries where there are robust electronic health record (EHR) systems which have nationwide data, some efforts have been made to use these data to identify patients with FH. Iceland has a unique repository of genotyping data available for 166,281 residents (44.6% of the population). Whole genome sequencing was performed for a subset of these records and FH was diagnosed based on the presence of pathogenic variants (prevalence 1:836) or based on clinical guidelines (prevalence much greater).[6] In Israel, a healthcare fund with integrated insurance and EHR data is available and contains medical information for approximately half of the population. From these data, MEDPED criteria were applied to diagnose patients with FH and the identified patients are followed to determine if and how FH was controlled. [32]

1.5.2 Perceived Barriers to Pediatric FH Screening

Screening efforts for FH have been met with varying levels of success and implementation. Some screening programs have illustrated the importance of multi-level structural support (e.g., government funding, acceptability in academic or clinical settings). For example, the importance of government facilitation and funding for the active screening process in the Netherlands was made apparent when it ceased to exist; the subsequent reduction in screening activities and FH diagnosis was evident.[5] Similarly, many of the FH registries rely on grant funding and coordination with clinicians to identify patients, which is not ideal for the longevity required for a disease like FH.[48,49,53]

Perhaps the most evident barrier to universal screening for FH in the US is the dissension in the guidelines given by different organizations. While the 2011 NHLBI guidelines are widely

supported and mirrored by other professional, medical, and public health organizations (as described in the previous section), they are contradicted by a recent statement published by the US Preventative Services Task Force (USPSTF).[28] This statement indicated that the USPSTF did not find sufficient evidence that universal childhood screening for FH was beneficial. However, one of their stated limitations that would inform some of these benefits was that they did not consider the potential effects of cascade screening in their literature search, which is an integral factor to the value of FH screening in childhood. The USPSTF review of FH literature was exceptionally strict and emphasized the use of randomized controlled trials (RCTs). As such, they had many sections in their review where they were unable to find any papers with relevant information[28]. While RCTs are a great source of scientific evidence, they are by no means the only source of valid and reliable evidence, especially in the context of public health initiatives like screening programs for inherited disease.

Another limitation in the literature is that there has not been a significant amount of published research on the perceptions and experiences of clinicians pertaining to what barriers exist to implementing screening for FH, especially pediatric lipid screening. Current data suggest that the children that do receive pediatric lipid screening are far more likely to be referred based on perceived risk for cardiovascular disease based on factors such as BMI, existing comorbid diagnoses, and known history of parental dyslipidemia.[14] Even for these patients who are perceived to be at-risk, more than half do not receive lipid screening or FH genetic testing.[14] This lack of screening in pediatric primary practice indicates that there may exist a lack of knowledge of FH, NHLBI guidelines, risks associated with long term elevated LDL-C for pediatric patients, or lack of understanding of the reasons for the importance of universal screening. Gathering data about how providers perceive FH, FH screening, and potential barriers to implementation may help to

bridge the gap in understanding between expert panels and everyday clinicians regarding universal pediatric lipid screening.

1.6 Bioethical Perspectives on Universal Pediatric FH Screening

The topic of population screening has long been debated among bioethicists, and adding the dimension of genetics to this topic makes it even more complex. The acceptability of a screening program from a bioethical perspective has long been based on the Wilson-Junger criteria (See Appendix B).[54] These criteria offer guidance on how to determine which conditions warrant screening based on the net benefit for the individual and the population. For example, the condition must be well-understood, have a treatment which is available and generally accessible, there should be a valid test that is cost-effective, and there should be a clear benefit from early identification.[54–56] With the advent of genetic screening programs and the discovery of rare but severe genetic diseases, there have been critiques of the Wilson-Junger criteria and their suitability for modern screening policy. Modifications to the original criteria have been proposed by modern bioethicists to improve the relevance and utility of the original criteria. For example, modern bioethicists recommend the consideration of extended benefits to family members of identified patients with genetic conditions from screening programs.[55] Additionally, the severe phenotypes of rare genetic diseases means that the diagnosis is an important goal, despite the potentially high costs of treatment or the small number of persons gaining benefits from the screening program.[55] Overall, they suggest that the sum of benefits ought to exceed the harms imposed by the screening program or subsequent diagnoses.[55]

One of the core ethical dilemmas of screening – and public health in general – is referred to as the "prevention paradox". The prevention paradox describes the tension between ethical principles of autonomy and beneficence brought on by activities like screening programs which restrict the autonomy of many but benefit only a few.[57] While screening programs will not benefit most of the individuals who are screened, the benefit conferred by the persons who are identified is substantial, and the restrictions on persons' autonomy who are not directly benefitted are generally not extreme. Additionally, the promotion of autonomy is not diametrically opposed to the implementation of universal screening programs. In fact, in pediatric populations, autonomy is already restricted to a significant extent, as their parents make medical decisions on their behalf. This may support the notion of pediatric universal screening further, as children demonstrably do not have the decisional capacity to autonomously decide to participate or not.[57] This may justify the use of expert guidance and scientific evidence as the basis for screening rather than autonomous decision-making alone.

Additionally, social and structural pressures may influence a person to participate when they otherwise would not.[57] Specifically, "mandatory" or "opt-out" screening may sometimes occur without total parental awareness due to the structural makeup of the program, as in the case of newborn screening. From a social pressure perspective, value judgements may be made with regards to the act of screening or the act of refusing to participate in a screening program. For example, a parent who might not wish to have their child screened for familial hypercholesterolemia in a community where awareness of FH and of pediatric lipid screening could be viewed negatively by their social peers because screening is seen as an imperative in the community to promote the health and well-being of their child. This social pressure may exert additional influence upon the parent to screen their child, bringing to question the degree of their

autonomy in their decision. Structural factors may also limit autonomy in the case of screening, and many critics of programs such as newborn screening argue that programs which are designed as "opt-out" deny parents informed consent for the testing.[57,58]

Pediatric screening in older children and adolescents has a unique dimension of respecting the autonomy of the child while still deferring to the parent for final medical decision-making. When determining if screening is ethically appropriate, one ought to consider the mental capacity of the child to understand what is being done and whether the child ought to instead have the right to make the decision themselves at an older age.[57] This deliberation should also examine the potential for reduced morbidity and mortality and future reproductive implications when determining if screening is warranted earlier versus waiting for the child to mature and make the decision themselves.

The ethical principle of non-malfeasance is also important when evaluating the ethical implications of pediatric universal screening. One issue that hearkens to this principle is the risk of false positives. Mathematically, as screening increases in scope there will be more false positive diagnoses. This means that a patient who does not truly have the condition would be incorrectly diagnosed with the condition. If a child was incorrectly diagnosed with FH based on screening results, this would mean there is a different underlying cause for their hyperlipidemia. The consequences of a false positive diagnosis vary in severity by condition. The consequences of a false positive diagnosis of FH would likely not be extreme, as the treatment for hyperlipidemia that is not due to FH is the same as the treatments for FH, if less aggressive. As such, false positives would still result in a benefit for the patient incorrectly diagnosed with FH. Notwithstanding, the structures of universal lipid screening programs are designed in a way that limits the risk of falsely diagnosing a child with FH, as the initial test is a lipid panel which is not specific for FH. Children

are only genetically tested for FH based on elevated LDL-C levels and a genetic test is not sufficient on its own to have a formal diagnosis given, as patients must meet other clinical diagnostic guidelines.

Human genomics is a fledgling field, and screening programs for genetic diseases have distinct ethical dilemmas from screening programs for non-genetic disorders. One of the most prominent ethical considerations regarding genetic and genomic testing is the highly personal nature of genomic data. This imbues a greater risk for breaches of confidentiality which could negatively impact a patient. Similarly, there are not as many legal protections for genetic disorders as for other conditions. The Genomic Information Non-Discrimination Act of 2008 (GINA) protects persons with genetic conditions from workplace and private health insurance discrimination but does not extend protections to other forms of insurance (life insurance, disability insurance, long term care insurance, federal health insurances).[59] Equally important is the provision in GINA that for patients with genetic conditions who already have symptoms of the condition are not extended the protections of GINA. This is an important factor to consider in the context of pediatric genetic screening, as carrying a genetic diagnosis may cause harm or hardship due to the lack of adequate legal protections for pre-existing genetic conditions, especially in the case of FH where LDL-C is elevated from birth. However, the Patient Protection and Affordable Care Act does offer protection for patients with pre-existing conditions more broadly, which helps to mitigate potential risks of early diagnosis of FH.[60]

The risk of incidental findings (discovery of a secondary condition which was not the target of the initial test) is also a consideration for the ethical acceptability of pediatric genetic and genomic testing. Targeted genetic testing like FH carrier testing or somatic genetic panels have a much lower risk of discovering incidental findings than genomic testing (testing of the entire

genome).[55,58] The risk of incidental findings in FH screening programs is low, as genetic testing is the second tier of the process and would be specific to the known pathogenic variant(s) identified in the index case.[12] A similar risk associated with any form of genetic testing is the potential to uncover situations of non-paternity in the process of reverse cascade screening. Incidental findings such as these may cause psychological stress or anxiety to the patient and their family. In genetic screening programs, there ought to be a conscientious effort to balance the competing interests of the child's health outcome and the familial impacts, positive and negative. Advocates refer to this attitude to genetic screening programs as a child-focused approach.[58]

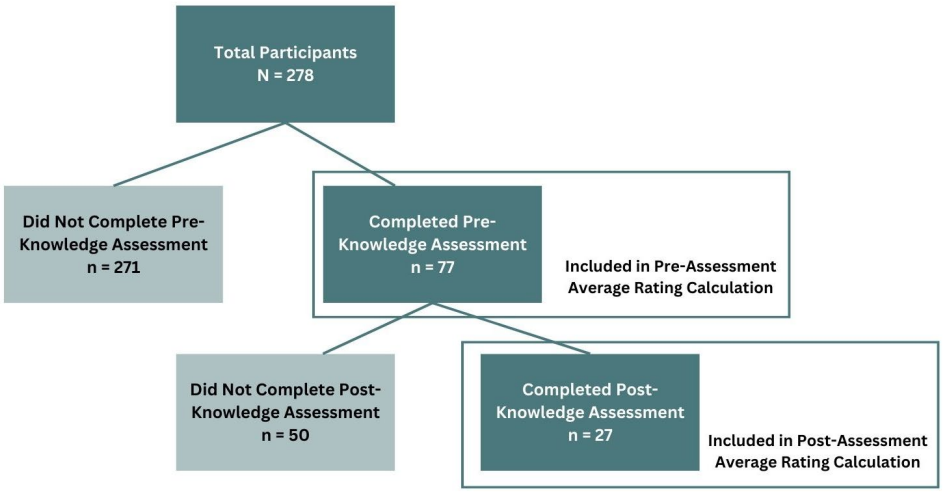
In the context of FH, the early detection and intervention made possible by pediatric screening has shown a significant impact in reducing morbidity and mortality associated with FH.[18,35] The benefits conferred onto additional persons after the identification of an index case through reverse cascade screening are also notable and may even allow for early intervention in parents or other close relatives who have not yet experienced premature cardiac events or manifested obvious clinical symptoms of cardiovascular disease.[17,18] As lipid panels can be non-fasting and ordered as a part of routine care at well-child checks or immunization visits, screening for FH does not pose an undue burden upon the general population, the healthcare provider, or the persons who are screened who do not have FH.[36,61] When evaluating all the ethical dimensions of pediatric screening for FH, it becomes apparent that the harms of not performing screening (i.e., premature atherosclerotic cardiovascular disease or death) are far greater in consequence than the harms or inconveniences associated with performing the screening (i.e., discovery of non-paternity). Furthermore, screening for FH in pediatric populations satisfies the Wilson-Junger criteria; FH is a well-understood condition, easy to test for, and there are accessible and effective treatments for FH which will yield measurable benefits given earlier intervention. The cost-

effectiveness of FH screening is also demonstrated to be positive, and the importance of FH as a condition is underscored by its classification as a CDC Tier 1 Genomics Application.[58,62]

2.0 Methods

Registration for the CEQI project was open to anyone who wished to participate. The learning series was advertised through the National Coordinating Center for the Regional Genetics Networks (NCC), the network of partners of the Midwest Genetics Network (MGN), the Family Heart Foundation (FH Foundation), the American Board of Pediatrics (ABP), the Midwest Clinicians Network, and the Ohio Academy of Family Physicians. IRB documentation for this project was obtained and is available in Appendix C. Upon registration, participants filled out a survey (see Appendix E for survey item information) reporting general demographic information and reasons for enrollment in the program. Primary role, practice affiliation, state of practice, clinical care time, and learning credit information were summarized using simple descriptive statistics. Survey data was gathered using Research Electronic Data Capture (REDCap) software. A Pre-Knowledge Assessment was given to all participants who indicated they sought MOC4 credits and/or PI points in their registration survey and was available but not required for participants seeking CME credit (n = 77). The Post-Knowledge Assessment was given as a part of the Cohort Closeout Survey for participants who completed the requirements for MOC4 credit or PI points, and two participants who sought CME credit (n = 27). The Pre- and Post- Knowledge Assessments were not linked for analysis. Figure 1 below shows the breakdown of how many participants completed each survey.

Figure 1: Survey Participation



The surveys asked a series of questions asking participants to rate their current 1) understanding of FH, 2) knowledge of pediatric lipid screening guidelines, 3) confidence implementing lipid screening in their own practice, 4) understanding of FH management strategies, and 5) confidence in FH management. Percent change was calculated based on the average ratings for the Pre-Knowledge Assessment and the Post-Knowledge Assessment. Average ratings were calculated by assigning ranked values to each Likert Scale response (Don't Know = 0, Poor = 1, Fair = 2, Good = 3, Excellent = 4). Significance testing was conducted using a Wilcoxon Signed-Rank test. Data analysis and visualization were conducted using Microsoft Excel, SPSS Statistics (version 29.0.2), and Canva Pro.

Qualitative analysis was performed on the two open-ended survey questions. The responses were coded to evaluate provider attitudes and behaviors regarding pediatric lipid screening and FH from participants completing quality improvement audit requirements. Codes were generated using thematic analysis coding methods. The coding was performed by the primary

author and subsequently reviewed and validated by a separate partner on the CEQI development team. The first code was used to categorize intended changes to the participant's practice based on what they learned in the CEQI project. The categories were determined to be: general improvement of screening (IS), improving screening specifically through universal screening strategies (IS-UNI), screening at an earlier age (IS-E), taking more detailed or conscientious family histories (FHx), patient education and/or outreach strategies (PO), education of colleagues or fellow providers (EDU), improvement of lipid profile screening documentation (DOC), use of resources from the VLCs or CEQI partners (RES), and increased confidence and/or feeling better informed on FH and lipid profile screening (INF). IS-UNI and IS-E were considered subcategories of IS and were counted both for the general IS category and their corresponding specific category. The key for this code is shown below in Table 4.

Table 4: Code Key for Change in Practice Qualitative Responses

Theme	Code
Improvement of screening (general)	IS
Implementation of universal screening	IS-UNI
Initiation of screening at earlier ages	IS-E
Taking improved family histories	FHx
Patient outreach and/or education	PO
Engaging/educating fellow providers	EDU
Improve documentation of lipid screening orders and/or results	DOC
Use of CEQI-provided resources	RES
Increased feelings of being better informed, increased feelings of confidence	INF

The second code was generated to categorize the overall takeaways and lessons learned reported by the participants. The categories for the general feedback code were determined as follows: nonspecific positive comments (POS-NS), endorsement of inclusion of family lived experiences (FAM-EXP), increased confidence prescribing statins or addressing statin hesitancy (STN), intention to make changes to clinical practice (CHG), importance of topic (IMPT), desire

for increased levels of detail (DET-INC), previous poor understanding of FH (PRE-POOR), desire to share the CEQI project with others (SHARE), content of project deemed useful (USE). A key for these codes is below in Table 5.

Table 5: Code Key for General Feedback Qualitative Responses

Theme	**Code**
Nonspecific positive comments on CEQI project	POS-NS
Endorsement/appreciation for affected family stories of lived experience	FAM-EXP
Increased confidence prescribing statins for pediatric patients or decreased statin hesitancy	DEC-HES
Intention to make changes to clinical practice to align with CEQI objectives	CHG
Comments on importance of topic	IMPT
Desire for greater detail about specific topics in the virtual learning sessions	DET-INC
Stated intent to share CEQI project and/or learned information with others	SHARE
Stated previous lack of knowledge regarding FH, screening, diagnosis, or management	PRE-POOR
Statement of utility of program content	USE

3.0 Results

In total, 278 registrants participated in the "Addressing FH" CEQI project. Most registrants were family practice physicians (20.5%, n = 57), pediatricians (15.1%, n = 42), nurse practitioners (17.3%, n = 48), nurses (11.2%, n = 31), and genetic counselors (12.2%, n = 34). There were registrants from 42 of the 50 US states, 4 US territories, and 6 countries. Of the registrants who reported regularly providing clinical care, 44.4% spent over 30 hours, 16.1% spent between 21-30 hours, 12.1% spent 11-20 hours, and 9.3% spent less than 10 hours providing clinical care each week. Specific demographic information is represented in Table 6 below, and a map of state-by-state participation for the US is available in Appendix D.

Table 6: Participant Demographics

Primary Role	Clinical Care Time	State of Residence			Other Residency
Advocate *n = 5*	< 10 hours per week 9.3%, *n = 26*	Alabama *n = 4*	Louisiana *n = 3*	Ohio *n = 6*	Guam *n = 1*
Educator *n = 4*	11-20 hours per week 12.1%, *n = 34*	Alaska *n = 0*	Maine *n = 1*	Oklahoma *n = 2*	Northern Mariana Islands *n = 1*
Family Practice Physician *n = 57*	21-30 hours per week 16.1% *n = 45*	Arizona *n = 5*	Maryland *n = 4*	Oregon *n = 0*	US Virgin Islands *n = 3*
Genetic Counselor *n = 34*	>30 hours per week 44.4%, *n = 124*	Arkansas *n = 1*	Massachusetts *n = 31*	Pennsylvania *n = 16*	Puerto Rico *n = 3*
Geneticist *n = 8*	Not applicable 17.5%, *n = 49*	California *n = 15*	Michigan *n = 10*	Rhode Island *n = 1*	Bangladesh *n = 1*
Nurse *n = 31*		Colorado *n = 3*	Minnesota *n = 8*	South Carolina *n = 8*	Canada *n = 1*
Nurse Practitioner *n = 48*		Connecticut *n = 6*	Mississippi *n = 1*	South Dakota *n = 1*	Mexico *n = 1*
Other Specialty Physician *n = 4*		Delaware *n = 0*	Missouri *n = 6*	Tennessee *n = 4*	Moldova *n = 1*
Pediatrician *n = 42*		Florida *n = 13*	Montana *n = 2*	Texas *n = 17*	Portugal *n = 1*
Physician Assistant *n = 14*		Georgia *n = 8*	Nebraska *n = 1*	Utah *n = 0*	Seychelles *n = 1*
Public Health Professional *n = 5*		Hawaii *n = 0*	Nevada *n = 2*	Vermont *n = 1*	
Research *n = 2*		Idaho *n = 4*	New Hampshire n = 6	Virginia *n = 12*	
Resident Physician *n = 15*		Illinois *n = 6*	New Jersey *n = 7*	Washington *n = 19*	
Student *n = 4*		Indiana *n = 8*	New Mexico *n = 3*	West Virginia *n = 0*	
Other *n = 5*		Iowa *n = 1*	New York *n = 10*	Wisconsin *n = 13*	
		Kansas *n = 1*	North Carolina *n = 5*	Wyoming *n = 0*	
		Kentucky *n = 1*	North Dakota *n = 0*		

Registrants were eligible to receive credit for their participation in the learning series. Most participants (59.5%, n = 195) registered for CME credit, with 7.9% (n = 26) registering for MOC2 credits, 7.0% (n = 23) registering for MOC4 credits, and 10.7% (n = 35) registering for PI points. Forty-nine registrants did not participate for credit. MOC2 credits, MOC4 credits, and PI points showed the highest rates of completion. CME credits had the lowest completion rate at 26.67%. A summary of credit data is given below in Table 7. Participants filled out different surveys according to the differing requirements for the respective credits they sought. Participants who registered for CME or MOC2 credit completed short surveys regarding the webinar learning objectives to obtain their credits but were not required to fill out the Pre- and Post-Knowledge Assessment surveys. Participants who sought MOC4 credit or PI points were required to complete the Pre- and Post-Knowledge Assessment surveys but were allowed to assign a group leader to complete survey data for participants from the same practice. As such not every person who sought and received MOC4 credit or PI points completed the surveys.

Table 7: Continuing Education Credit Registration and Completion

Credit Type	Credit Sought	Credit Awarded	Credit Completion Rate
CME	59.5%, n = 195	n = 52	26.67%
MOC2	7.9%, n = 26	n = 14	53.85%
MOC4	7.0%, n = 23	n = 9	39.13%
PI	10.7%, n = 35	n = 16	45.71%
Not Participating for Credit	14.9%, n = 49		

Of the 77 participants who completed the Pre-Knowledge Assessment, a cohort of 27 (35.1%) also completed the Post-Knowledge Assessment for MOC4 credit or PI points. This cohort provided qualitative feedback for the program in each audit cycle and in the Closeout

Survey at the end of the learning series. In the Pre-Knowledge Assessment, no participants indicated “Excellent” knowledge or confidence for any of the survey questions. Interestingly, the inverse pattern was seen for those who completed the Post-Knowledge Assessment; no participants indicated “Poor” or “Don’t Know” in their responses for any of the survey questions in the Post-Knowledge Assessment. The observed increases in reported ratings for each of the survey questions was shown to be significant ($p < 0.001$, $\alpha = 0.05$) using a Wilcoxon-Signed Ranks test.

Before the program, a substantial portion of the participants rated their understandings of FH and of pediatric lipid screening guidelines as “Poor” or “Fair” (15.6%, 53.2%). After participation, all members of the cohort who completed both surveys reported “Good” or “Excellent” (48.1%, 51.9%) understanding of FH and pediatric lipid screening guidelines. This represented a 39.8% increase in the average rating of FH by participants after the learning project. A similar trend was seen when participants were asked to rate their understanding of FH management. Before the program, most indicated “Don’t Know”, “Poor” or “Fair” understanding of FH management (6.5%, 25.9%, 40.3%). However, there were a few respondents (27%, $n = 21$) who indicated “Good” understanding of FH management practices before participating in the CEQI project. After the project, most participants rated “Good” or “Excellent” understanding of FH management (48.1%, 37.0%), but 4 participants (14.8%) still indicated having only a “Fair” understanding. Despite some participants continuing to rate their understanding of FH management recommendations relatively low, there was a substantial observed increase in the average rating (41.6%). This indicates that compared to the pre-knowledge assessment, the average understanding of FH management recommendations increased substantially from generally low to generally high.

There was also an observed increase in confidence ratings for the implementation of pediatric lipid screening guidelines and managing FH in practice. In the Pre-Knowledge Assessment, only a small portion of the respondents rated high levels of confidence implementing pediatric lipid screening guidelines or managing FH in their own patients. After participation in the CEQI project, almost all reported high levels of confidence screening for and managing FH in their own practices, with an observed percent change in average ratings of 47.0% and 39.7% for screening and management, respectively. Chart audit data also showed that after participation, 73.0% of the next ten patients seen by each of the participants had lipid profiles ordered for FH screening. Wilcoxon-Signed Rank tests were conducted in SPSS for each of the assessment questions, and all showed a highly significant increase in reported ratings of confidence and understanding ($p < 0.001$). The responses from the Pre- and Post-Knowledge Assessment surveys are listed below in Table 8.

Table 8: Provider Knowledge and Attitudes Regarding FH Before and After Participation

Survey Question	Rating										Average Rating Percent Change	Wilcoxon-Signed Rank Test
	Poor		Fair		Good		Excellent		Don't Know			Test statistic (Z) $\alpha = 0.05$
	pre	*post*	*pre*	*post*	*pre*	*post*	*pre*	*post*	*pre*	*post*		
Understanding of FH	12 (15.6%)	0 (0%)	41 (53.2%)	0 (0%)	23 (29.9%)	13 (48.1%)	0 (0%)	14 (51.9%)	1 (1.3%)	0 (0%)	+39.8%	Z=4.378, p<.001
Understanding of Pediatric Lipid Screening Guidelines	22 (28.6%)	0 (0%)	27 (35.1%)	0 (0%)	19 (24.7%)	6 (22.2%)	1 (1.3%)	21 (77.8%)	8 (10.4%)	0 (0%)	+52.9%	Z=4.369, p<.001
Confidence Implementing FH Pediatric Lipid Screening Guidelines	19 (24.7%).	0 (0%)	29 (37.7%)	2 (7.4%)	20 (25.9%)	8 (29.6%)	2 (2.6%)	17 (63.0%)	7 (9.1%)	0 (0%)	+47.0%	Z=4.299, p<.001
Understanding of FH Management Recommendations	20 (25.9%)	0 (0%)	31 (40.3%)	4 (14.8%)	21 (27.3%)	13 (48.1%)	0 (0%)	10 (37.0%)	5 (6.5%)	0 (0%)	+41.6	Z=4.011, p<.001
Confidence Implementing FH Management Recommendations	17 (22.1%)	0 (0%)	23 (29.9%)	3 (11.1%)	26 (33.7%)	13 (48.1%)	3 (3.9%)	11 (40.7%)	8 (10.4%)	0 (0%)	+39.7%	Z=3.602, p<.001

Seven general themes were identified from participants' qualitative responses to the survey prompt: "Please describe the changes you made in your practice as part of this quality improvement audit cycle." This question was given to participants upon the completion of each audit cycle. The most common theme identified was the intent to improve screening for FH in their pediatric patients. This theme was subdivided into responses which specified that the participant intended to 1) initiate screening at an earlier age, and/or 2) implement universal screening for their patients according to NHLBI guidelines. Another theme identified was a stated intent to improve the obtainment of family histories for their patients. This included intents to update family histories, gather specific information on family history of cardiovascular disease, and pay closer attention to family history information when seeing patients for routine visits. Participants also reported making efforts to engage with patients and their families to educate them on the importance of pediatric lipid screening, identification of FH, and better prepare them for the screening process.

Similarly, several participants reported efforts to educate their fellow providers about FH and the importance of pediatric lipid screening. Some also reported that in discussion with their colleagues, a practice-wide policy was established to universally screen children aged 9-11 for FH. Some participants also specifically mentioned the use of resources from the CEQI project or the Family Heart Foundation as tools to educate families when doing patient/family outreach and when sharing information with their peers. Another theme seen in responses was intent to improve documentation of FH screening efforts in patient charts, including when a lipid panel was ordered, if parents refused a lipid panel, and when results were received, including normal results. Finally, participants reported positive changes in their attitudes regarding their understanding of FH and feelings of preparedness to have discussions with families about pediatric lipid screening and FH. Only 2 participants answered that they would not make changes to their existing practice after

participation in the virtual learning series. These two participants were then prompted in the survey to identify barriers to the implementation of changes. In this survey question, both indicated that changes would reinforce what they already do in their practice, and the other identified patient non-compliance with obtaining lipid panels as a barrier to universal screening in their practice. One indicated internal systems-level barriers existed to making changes in their practice. Frequencies of the mentions of the described themes in participant responses from each audit cycle are contained below in Table 9. Participants were able to describe multiple intended changes in their responses, so n > 27 in this table.

Table 9: Reported Changes to Practice in setting of CEQI Participation

Theme	CODE	Cycle 1	Cycle 2	Cycle 3
Improvement of screening (general)	IS	19	19	20
Implementation of universal screening	IS-UNI	7	6	5
Initiation of screening at earlier ages	IS-E	4	4	5
Taking improved family histories	FHx	7	4	8
Engaging/educating fellow providers	EDU	2	2	3
Patient outreach and/or education	PO	8	9	5
Improve documentation of lipid screening orders and/or results	DOC	3	3	2
Use of CEQI-provided resources	RES	0	2	1
Increased feelings of being better informed, increased feelings of confidence	INF	4	3	5

Participants were also able to give overall feedback in the project closeout survey regarding their attitudes towards FH, pediatric lipid screening, and the project as a whole. These responses were coded according to 9 themes identified in the survey responses. One theme in the responses was general positive feedback on the learning program without specifics (POS-NS). One of the more specific themes identified was comments stating appreciation for or which highlighted the perceived value of included testimonials from an affected family with FH (FAM-EXP):

1) *"I loved hearing the personal stories of familial hypercholesterolemia"- Participant 185*

2) *"Including the lived experience of this family was invaluable. The clinical information was presented clearly as well. Excellent session!" – Participant 8*

Similarly, several participants commented on their perceived importance of FH as a topic and as a medical condition to be considered in their practice (IMPT). Furthermore, there was also a trend of responses where participants commented on their knowledge gained through the experience and/or their previous poor or limited understanding of FH and pediatric lipid screening (PRE-POOR). Participants also reported a greater level of confidence and understanding regarding the use of statins as a frontline treatment for FH in pediatric patients. Also in this theme were comments on participants' decreased hesitancy prescribing statins and increased feelings of their ability to combat statin hesitancy in their peers or parents of their patients (DEC-HES). One response that illustrates several of these themes this is provided in its entirety below:

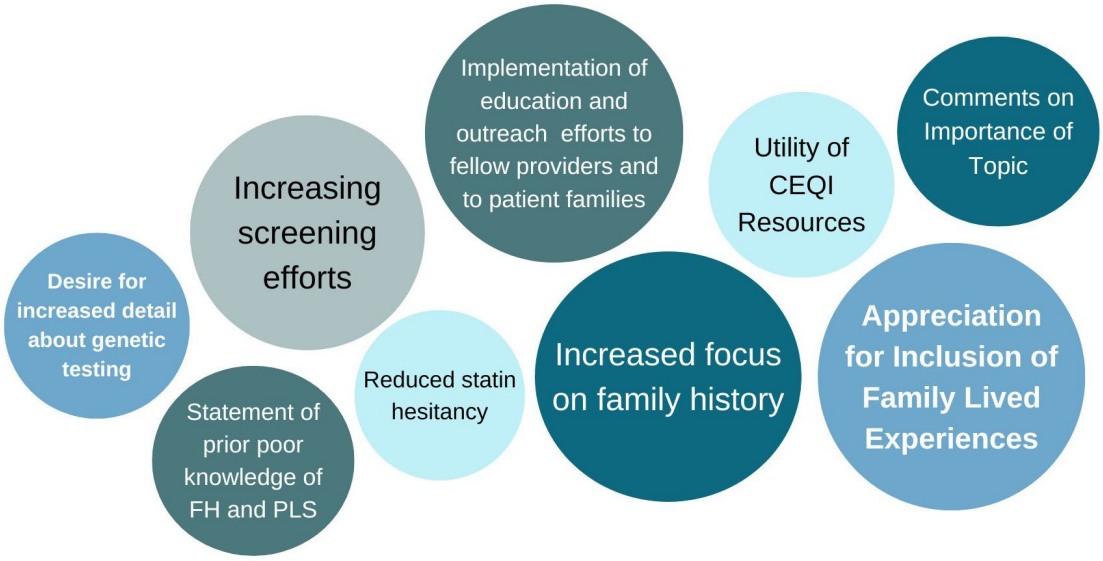
"As a family practice doctor[sic] I knew about the recommendation to screen kids with lipids at age 9-11, but I have truthfully never done it in my practice before. This presentation helped me better understand the reasoning and importance behind screening and I plan to start immediately. I prescribe statins all the time in adults, but have not in children. I appreciate all of the discussion about safety and importance of using these meds in children in the correct situation. I do feel comfortable in managing this in my practice after this series." – Participant 229

Participants also frequently commented on the perceived usefulness of the program and its content (USE). Many participants also stated an intent to share the information gained through this process with their fellow practitioners and with the families that they see in their daily practice to raise awareness of FH and the importance of achieving universal screening for FH in pediatric populations (SHARE). For example:

1) *"This presentation and the whole series have been excellent. I wish all pediatricians would access this education and provide universal screening." – Participant 8*
2) *"Practical and informative as well as practice changing." – Participant 290*
3) *"Overall great education, information, and resources provided. Enjoyed the PI project as it provided me with increased confidence in treating pediatric patients given an overall low pediatric patient volume within the area and my current practice." – Participant 47*

While feedback was generally positive, there was a trend of responses which stated a desire for more detailed information about the technical aspects of FH screening (DET-INC). Participants stated a desire to know more about the genetic testing aspect of screening and the initiatives that exist to support achieving universal screening for FH. Constructive feedback also included the desire for more detail about side effects of long-term pediatric statin usage and tools to better understand what to do in the situations where patients experience side effects. The themes in participant attitudes regarding FH and the CEQI project are illustrated below in Figure 2.

Figure 2: Reported Changes in Participant Attitudes Regarding FH



4.0 Discussion

This study demonstrated that pediatric healthcare providers generally have a low baseline level of knowledge regarding FH. Based on survey responses from this virtual learning project, it seems that pediatricians and family medicine physicians are not aware of FH as a condition or of the risks associated with missed early diagnosis opportunities. Previous research into FH has not focused specifically on the knowledge of FH among pediatric care providers, but studies which examine screening rates for FH demonstrate that FH diagnosis does not seem to be a priority for primary care physicians in the United States, even among children who demonstrate high risk for the condition.[13,14,31] Historically, research into the diagnosis and management of FH has centered around adult patients with FH, with some studies even excluding pediatric providers from participation.[38] As such, this paper provides novel insight into the knowledge and perceptions of FH among pediatric providers.

While not specific to FH, some studies have explored primary care physicians attitudes and knowledge with genetic testing more broadly. As recently as 2019, a survey found that the majority of physicians have poor genetic literacy, and over half never received any formal genetics or genomics education.[63] This same survey found that among the same group, few felt comfortable discussing genetics with their patients, in contrast to having high levels of confidence discussing other health subjects.[63] This aligns with our findings that pediatric providers have poor understanding of FH and low levels of confidence screening or implementing treatment for FH. Similarly, there were no references to existing universal pediatric genetic screening programs (i.e., newborn screening), which may support previous findings that genetic literacy overall for providers is relatively poor. These findings are also supported by previous literature which found

that providers are not comfortable at baseline prescribing pharmacological treatments to their pediatric patients with FH, despite published recommendations.[36,38,45,64] Furthermore, the observed lack of knowledge regarding FH extends to pediatric hyperlipidemia in general, as it has been shown that pediatric providers are not familiar with the normal range of lipid levels for children.[36]

Overall, this program was shown to be effective at increasing knowledge and confidence regarding FH and pediatric lipid screening for FH among a population of US physicians. (knowledge of FH, knowledge of pediatric lipid screening guidelines, understanding of FH treatment, confidence implementing pediatric lipid screening, and confidence managing FH) in the Knowledge Assessments given before and after participation in the CEQI project, there was a significant ($p<0.001$) increase in self-reported ratings.

As mentioned previously, little research has been done regarding improving awareness and screening practices for FH, but previous research has shown that improving awareness and genetic literacy for other CDC Tier 1 Genomics Applications, namely Hereditary Breast and Ovarian Cancer (HBOC), can lead providers to make changes in their practice to improve detection.[65] The format of this program differed significantly from the delivery of the FH educational program. The HBOC learning program was a self-directed online module-based program, whereas the FH project (although recorded and available asynchronously) was delivered as three interactive webinars. In the FH learning program, 96% of the respondents in this study indicated that they would make changes to their practice based on the knowledge gained through their participation in the virtual learning program.

Previously mentioned studies of interventions to improve general provider genetic literacy support participatory or interactive learning in virtual learning opportunities to be effective methods to increase provider confidence.[63] In the case of this study, we also observed an increase

in ideal screening behaviors. Compared to the HBOC program, where approximately half of the participants reported an intent to change practice, it seems to indicate that interactive learning may be more effective.[65] This is supported by other literature which demonstrated that interactive learning programs to build awareness of a condition improves rates of screening.[66] For example, it is recommended by both the AAP and the USPSTF that children with systemic lupus erythematosus (c-SLE) should be universally screened for depression, but actual rates have been measured to be only about 2%. This problem parallels the dilemma of achieving universal pediatric screening for FH. A study of an interactive intervention to increase awareness and the incorporation of screening into everyday practice was highly effective, increasing the studied clinic's screening rate from 3.3% to 80%.[66] This mirrors the findings in our own study, where 96% of respondents indicated that they intended to make changes to their practice based on the knowledge gained through their participation in the virtual learning program and a screening rate of 73.0% was observed following the program.

Considering this in conjunction with the measurable and significant increases in provider knowledge and confidence, this may indicate that increased understanding and familiarity with FH and pediatric lipid screening guidelines could lead to increased rates of screening in practice. Specifically, participatory methods of increasing pediatric provider knowledge regarding screening and FH might facilitate narrowing of the wide gap between current screening rates (approximately 20%) and the goal of universal screening.[13,14,36] Aside from increasing screening efforts, intended changes to practice reported by participants emphasized intentional communication strategies. Specifically, an emphasis on taking deliberate care when taking family histories for their pediatric patients was observed. Participants reported an increase in their perceived importance of family history information, especially regarding any premature

cardiovascular disease in family members. Previous studies have found similar relationships between the level of a provider's genetic literacy and their perceived importance of family history information.[63] A few participants also stated that for children whose family history is unknown (e.g., children in foster care or who have been adopted) they would begin screening at age 2 to prevent late diagnosis of potential HoFH.

Participants' emphasis on communication strategies to improve practice also manifested as stated desire to share the information they learned with not only their patients but also their fellow providers. This included plans to present on FH and pediatric lipid screening guidelines to their colleagues as well as intentional outreach to parents of patients before, during, and after patient appointments. This desire of participants to spread awareness of FH has not been documented previously in published literature. Changes in communication strategies also included engagement in deeper educational discussions with parents about the importance of pediatric lipid screening, especially for patient families with a strong indication for FH. One participant even reported that their practice began introducing the concept of lipid panel screening in phone messages prior to routine visits. Furthermore, many responses indicated that participants felt they gained valuable practical knowledge through their participation and found the knowledge imparted in the virtual presentations to be generally important. The emphasis on improved communication strategies extended to stated intentions to improve documentation of the screening process in patient charts, even when results were in the normal range. These themes identified in participant responses indicate that while pediatric providers may not have a high level of familiarity with FH or understanding of pediatric lipid screening guidelines, they do find education to be valuable and effective at improving their knowledge and increasing their intention to implement universal lipid screening in their practices. This finding is supported by measured outcomes both in this study and

in previous literature regarding medical education for genetics and screening practices.[63] Overall, this may indicate that while pediatric providers may not have a high level of familiarity with FH or understanding of pediatric lipid screening guidelines, they do find education to be valuable and effective at improving their knowledge and increasing implementation of universal pediatric lipid screening in their practices.

Feedback from participants regarding this educational opportunity was overwhelmingly positive. Notably, participants did not raise any ethical objections to the practice of pediatric lipid screening for FH in their feedback for the program. While the surveys did not specifically address ethical considerations behind pediatric lipid screening, the overwhelming trend in responses was that pediatric care providers simply did not perceive FH as an important public health problem prior to participation in the program. One factor that many participants reported as having a strong impact to increase their perceived importance of early detection of FH was the inclusion of a presentation of lived experiences of a family with FH given by a family advocate who shared the impact that early detection had for their family. Previous educational programs have included similar information in the form of case reports,[65] but the personal nature of the presentation may have increased the impact on participant attitudes towards FH and pediatric screening for FH.

Allusions were made to ethical concerns regarding the use of statin drugs and other pharmacologic treatments in pediatric patients, which has been discussed in the context of statin hesitancy. However, feedback from the program regarding statin hesitancy showed that education about FH and the safety, efficacy, and essential nature of pharmacological treatments for pediatric patients with FH decreased statin hesitancy and increased confidence managing FH in pediatric patients. Other investigations into provider recommendations for FH treatment have also found a

pattern of statin hesitancy which can be ameliorated through education, however prescribing behaviors have not been observed to increase by a great degree.[37,38]

Participants in this virtual learning series demonstrated a high degree of openness to learning and education with regards to FH and pediatric lipid screening. Notably, 100% of respondents stated they would recommend the learning series to a friend or colleague, and 100% reported that they found the project to be a valuable use of their time. The positive feedback regarding the CEQI project indicates that in addition to being effective, the format is acceptable to the target population. This is important to consider, as previous studies have found that the vast majority of providers, in addition to not having formal genetics training, also have not participated in informal genetics education programs such as the one studied in this project.[63] Some participants did express a desire for future programs to include more information on the genetic etiologies of FH and specific information regarding the process of genetic testing and cascade screening that occurs after a positive result. These responses further support the assertion that the format is acceptable to participants, and that pediatric providers who may not have high levels of genetic literacy do welcome opportunities to improve their understanding of common genetic conditions.

This may further support the notion that learning opportunities such as the CEQI project "Addressing Familial Hypercholesterolemia" are appropriate interventions to increase awareness of FH and pediatric lipid screening guidelines to subsequently increase screening rates in pediatric populations. This information may be instrumental for the narrowing of the gap in universal screening guidelines and actual screening rates. It would be valuable to know in more detail what makes the format acceptable to the target audience (pediatric primary care providers). For example, some factors which may have a role in the accessibility and acceptability might be virtual delivery, availability of webinars to watch live or asynchronously, and no registration cost. Usage for the

aforementioned study regarding continuing medical education for HBOC was tracked, and showed that the resource, which was also offered virtually and asynchronously, was highly utilized by participants.[65] This may offer additional support for virtual and asynchronous availability yielding increased accessibility and acceptability for providers seeking to improve their genetics knowledge.

Overall, these findings support the notion that primary care providers for pediatric patients welcome learning about FH and pediatric lipid screening, and that they are open to making changes in their everyday practice to bring the goal of universal screening closer to reality. Findings suggest that participatory learning methods and interpersonal communication to raise awareness of FH and pediatric lipid screening guidelines is an effective and agreeable method to increase the likelihood that a provider will be able to universally screen their patients for hyperlipidemia and FH.

4.1 Limitations

There were a few notable limitations for this project. One of the largest limitations was that Pre-Knowledge Assessment and Post-Knowledge Assessment surveys were not available to all participants. Only those who indicated they wished to receive credit for participation completed the Pre-Knowledge Assessment and only those who wished to obtain MOC4 credit or PI points completed the Post-Knowledge Assessment and Closeout Surveys. As such, this limited our ability to observe changes in knowledge in the setting of the virtual learning series and reduced the amount of available data substantially. Surveys being selectively given according to credit requirements resulted in the cohort sample being comprised of all physicians located in the United States. This also limited the amount of qualitative data which was collected, meaning that conclusions drawn

about provider attitudes regarding FH and pediatric lipid screening may not be representative of the broader group of primary care providers who might be responsible for ordering lipid profiles (e.g., nurses, nurse practitioners, physician assistants), and also represents a missed opportunity for data on international perspectives pertaining to FH and universal pediatric lipid screening.

An additional limitation for this study encountered was that a key survey question about perceived barriers to implementing was only shown to 2 participants due to branching logic in the survey software. More information on this specific topic would have been invaluable to gain a more holistic perspective on provider attitudes toward universal pediatric lipid screening and may have offered more nuanced insight into why providers may not be ordering lipid profiles for all of their pediatric patients at the recommended ages. In the future, it may be more useful to include this question as a part of the Pre- and Post-Knowledge Assessments for all participants.

There was a moderate amount of loss to follow up for the participants who initially registered for credit but did not complete the requirements (i.e., surveys). Only 41.34% of participants registered for credit for participation actually completed the requirements to receive credit. The completion rate was higher than the mean for MOC4 and PI credit (39.13%, 45.71%), but many did not complete audits or requirements. There may be self-selection bias in the cohort of participants who did complete all the requirements, as those who were more likely to complete the quality improvement requirements may generally be more likely to be amenable to making changes in their practice than the participants who did not. Similarly, participation in the project was completely voluntary and there may be some self-selection bias due to people who are already interested in FH or pediatric dyslipidemias being more likely to register for the virtual learning series.

4.2 Future Directions

Future cycles of this program should incorporate more knowledge assessments and feedback opportunities for all registrants, regardless of the potential learning credits they may seek for their participation in the project. Specifically, to gain a more complete view on providers attitudes regarding FH, all registrants should complete Pre- and Post-Knowledge Assessments in addition to the demographic details surveyed at registration. As mentioned in the limitations, it would also be invaluable to include survey items about barriers to implementation of universal pediatric lipid screening as a part of these surveys that are given to all providers. With this data, it would be interesting to investigate whether there are any categorical differences in attitudes or perceptions regarding FH and/or pediatric lipid screening between types of primary care providers (e.g., physicians vs. physician assistants vs. nurse practitioners vs. nurses, etc.).

5.0 Conclusions

This study has demonstrated that not only are virtual participatory learning programs effective at increasing knowledge of FH and pediatric lipid screening guidelines, but also at effecting practice changes among providers who participate. Furthermore, this program was demonstrated to be an acceptable method for the delivery of information regarding FH and the importance of screening for FH in pediatric patient populations. Findings in this study suggest that a lack of knowledge of FH may be a substantial contributing factor to observed low rates of pediatric lipid screening in the United States. This was demonstrated in a substantial observed increase in participant self-rated understanding and confidence regarding FH diagnosis and management and in screening behaviors in practice after participation in the learning project. The theme of a desire to spread awareness of FH among both peer and patient populations in particular suggests that lack of knowledge may underlie low screening guideline adherence by pediatric providers. Late and underdiagnosis of FH is an urgent public health problem that affects 1 in approximately 250 people worldwide, and identifying patients with FH before they suffer premature cardiovascular morbidity or mortality is critical to improving their longevity and quality of life. It is critical to understand the attitudes of primary care providers and their understanding of pediatric lipid screening for FH as an importance public health practice in order to devise interventions which are appropriate, acceptable, and effective. Future research should specifically address the barriers to implementation of pediatric lipid screening perceived by pediatric providers to provide a more complete understanding of the attitudes and behaviors of pediatric providers regarding FH and pediatric lipid screening.

6.0 Permissions and Original Creations

Survey data for this thesis project was shared with the author by the Michigan Public Health Institute Center for Strategic Health Partnerships as a part of their Visiting Scholar program. All participants consented to the use of their deidentified survey response data for reporting and analysis. This project is supported by the Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services (HHS) as part of an award totaling $907,701.00 with 0% financed with non-governmental sources. This information, content or conclusions are those of the author(s) and do not necessarily represent the official views of, nor an endorsement by, HRSA, HHS or the U.S. Government. For more information, please visit www.HRSA.gov.

Appendix A FH Diagnosis Criteria

Appendix A.1 Make Early Diagnosis to Prevent Early Death (MEDPED)[25,67]

Table 10: MEDPED Diagnosis Guidelines

Patient Age (years)	1st-Degree Relative Cholesterol Level	2nd Degree Relative Cholesterol Level	3rd-Degree Relative Cholesterol Level	General Population (Patient Cholesterol Level)
< 18	220 mg/dL total or 155 mg/dL LDL-C	230 mg/dL total or 165 mg/dL LDL-C	240 mg/dL total or 170 mg/dL LDL-C	270 mg/dL total or 200 mg/dL LDL-C
20-29	240 mg/dL total or 170 mg/dL LDL-C	250 mg/dL total or 180 mg/dL LDL-C	260 mg/dL total or 185 mg/dL LDL-C	290 mg/dL total or 220 mg/dL LDL-C
30-39	270 mg/dL total or 190 mg/dL LDL-C	280 mg/dL total or 200 mg/dL LDL-C	290 mg/dL total or 210 mg/dL LDL-C	340 mg/dL total or 240 mg/dL LDL-C
≥40	290 mg/dL total or 205 mg/dL LDL-C	300 mg/dL total or 215 mg/dL LDL-C	310 mg/dL total or 225 mg/dL LDL-C	360 mg/dL total or 260 mg/dL LDL-C

Diagnosis of FH: Total or LDL-C levels exceed above thresholds based on patient age

Appendix A.2 Simon Broome[25]

For DEFINITE FH:

- Total cholesterol ≥ 290 – adults, 260 mg/dL – children (under 16 years old) OR LDL-C > 190 mg/dL – adults, 155mg/dL – children

AND

- Presence of tendon xanthomas in patient or close relatives (first or second degree)

OR

- Presence of pathogenic mutation in *LDLR, APOB,* or *PCSK9* genes

For PROBABLE FH:

- Presence of tendon xanthomas in patient, 1st-, or 2nd-degree relative

For POSSIBLE FH:

- Family history of:
  - Total cholesterol ≥ 290 – adult relative, 260 mg/dL – child relative (including siblings or children of patient) (under 16 years old) OR LDL-C > 190 mg/dL – adult relative, 155mg/dL – child relative
  - Myocardial infarction < 50 years of age in 2nd-degree relative, < 60 years of age in 1st-degree relative

Appendix A.3 Dutch Lipid Clinic Network[25]

1. Family History
   - 1st Degree Relative with premature cardiovascular disease (male <55, female <60) (1 point)
   - 1st Degree Relative with known LDL-C ≥ 95 percentile (2 points)
   - Child (age ≤18) with known LDL-C ≥ 95 percentile (2 points)
   - 1st Degree Relative with tendon xanthomas or arcus cornealis (2 points)
2. Clinical History
   - Patient with premature coronary artery disease (male <55, female <60) (2 points)
   - Patient with premature cerebral or peripheral vascular disease (1 point)
3. Physical Signs
   - Tendon xanthomas (6 points)
   - Arcus cornealis before age 45 (4 points)
4. LDL-C Levels

- >325 mg/dL (8 points)
- 251-325 mg/dL (5 points)
- 191-250 mg/dL (3 points)
- 155-190 mg/dL (1 point)

5. Genetic Testing
    - Pathogenic Mutation in *LDLR, APOB,* or *PCSK9* genes (8 points)

Definite FH: Score ≥ 8 points

Probable FH: Score 6-8 points

Possible FH: Score 3-5 points

Unlikely FH: ≤ 2 points

Appendix A.4 European Atherosclerosis Society[20,35]

Diagnosis of FH in Children:

- LDL-C remains > 190mg/dL after 3 months of diet and lifestyle changes
- LDL-C >160 mg/dL **AND**
    - Family history of premature cardiovascular disease **OR**
    - Parent with untreated elevated cholesterol
- LDL-C > 130 mg/dL **AND** parent with genetic diagnosis of FH
- Positive genetic test for known pathogenic mutation causing FH

Recommendation of 2 LDL-C measurements over period of 3 months.

Appendix B Wilson-Junger Criteria[54,55]

- Condition is an important public health problem.
- Acceptable treatment exists.
- Facilities for diagnosis and treatment are available.
- Suitable test exists.
- Test is acceptable to the population.
- Natural history of condition is well-understood.
- There is an identifiable pre-clinical stage to the condition
- Case finding is cost-effective relative to potential medical costs from condition if left undetected.
- Case-finding efforts are ongoing.

Appendix C IRB Documentation

Supplemental File 1: https://d-scholarship.pitt.edu/46254/1/IRB%20Approval%20Documentation.pdf

PDF (IRB Documentation)
Supplemental Material
Download (86kB)

Appendix D Additional Participant Demographics

Figure 3: Chloropleth Map of US Participant Residency

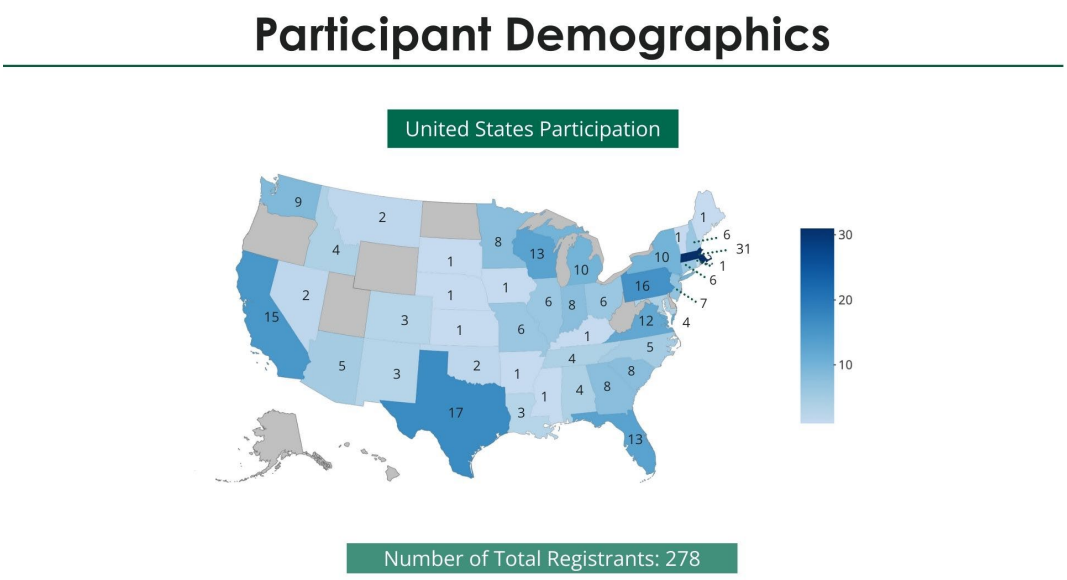


Figure 4: International Participation

Appendix E Survey Questionnaires

Supplemental File 2: https://d-scholarship.pitt.edu/46254/2/PreKnowledgeAssessment_Address.pdf

PDF (Pre-Knowledge Assessment)
Supplemental Material
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Supplemental File 3: https://d-scholarship.pitt.edu/46254/3/CohortCloseoutSurvey_Addressin.pdf

PDF (Post-Knowledge Assessment (Closeout))
Supplemental Material
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