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REVIEW

The Role of Reverse Cascade Screening in Children with Familial Hypercholesterolemia: A Literature Review and Analysis

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Abstract

Purpose of Review Familial Hypercholesterolemia (FH) is a common genetic disorder characterized by lifelong elevation of severely elevated plasma low-density lipoprotein cholesterol. Atherosclerotic cardiovascular disease (ASCVD) risk accelerates after age 20. Early diagnosis allows for treatment of children with FH and creates an opportunity to identify affected relatives through reverse cascade screening (RCS). Historically, cascade screening has had little impact on identifying individuals with FH.

Recent Findings Universal cholesterol screening (UCS) to identify youth with FH, beginning at 9–11 years-of-age, is currently recommended in the U.S. The European Atherosclerosis Society has called for UCS worldwide, emphasizing the need for educational programs to increase awareness amongst healthcare professions. Underdiagnoses and undertreatment of FH remain high. Improved rates of UCS and a systematic approach to RCS are needed.

Summary The absence of a coordinated RCS program limits the benefits of UCS. Further research is needed to identify barriers to cholesterol screening in youth.

Keywords Familial Hypercholesterolemia · Reverse Cascade Screening · LDL-C · Hyperlipidemia · Universal Cholesterol Screening

Introduction

Familial Hypercholesterolemia (FH) is an autosomal codominant genetic disorder which results in premature cardiovascular disease (CVD) secondary to lifelong exposure to atherogenic lipoproteins. Although common, heterozygous FH (heFH) is underdiagnosed and under recognized throughout most of the world. This is due, in part, to the difficulty of differentiating FH from other causes of hyperlipidemia during adulthood, but also low rates of cholesterol screening, particularly in youth. While FH can be diagnosed clinically using a variety of scoring systems, genetic testing remains the gold standard. Although atherosclerosis is present from an early age, the vast majority of children with heFH are asymptomatic. Thus, UCS is critical in identifying those with FH who would benefit from early intervention. Furthermore, UCS creates an opportunity of identifying affected relatives through RCS, a screening method that has been utilized successfully in many European countries. Prior forms of cascade screening based upon 1) selective rather than universal screening during childhood or 2) screening related to ASCVD-related events during adulthood have not been effective in diagnosing FH. Combined, UCS and reflex RCS has the potential for identifying most adults and children with FH.

Overview of Familial Hypercholesterolemia

Pathophysiology and Prevalence

FH results from variants of genes which control low-density lipoprotein (LDL) uptake, leading to premature CVD [1]. Initially described in 1986 as a defect in the LDL receptor (LDLR) [2], FH is now known to be caused by variants in at least four genes [3]. More than ninety percent of cases are a

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result of *LDLR* gene defects, variants of genes for apolipoprotein B (*APOB*), protein convertase subtilisin/kexin type 9 (*PCSK9*), and LDLR associated protein 1 (*LDLRAP1*) accounting for the remainder [4, 5]. There are 2,104 known unique variants of *LDLR, APOB, and PCSK9* associated with FH, 1,097 of which are categorized as pathogenic or likely pathogenic [6, 7]. However, in the vast majority of individuals with an FH phenotype, a pathogenic variant cannot be identified [8, 9]. Irrespective of whether a causative gene is identified, decreased LDLR activity contributes to increased circulating low-density lipoprotein cholesterol (LDL-C) levels by reducing hepatocyte uptake of LDL. This stimulates hepatic LDL production due to low intracellular concentration of free cholesterol. The lifetime exposure to atherogenic lipoprotein greatly increases the risk of CVD and premature mortality.

The prevalence of heFH varies by region and population. A recent meta-analysis of 42 studies with over 7.3 million participants found the prevalence of heFH to be 1:311 in the general population [10], while a previous review of 19 studies and 2.5 million participants reported 1:250, although the latter study did not exclude populations with a founder effect, perhaps resulting in a higher estimated prevalence [11]. In founder populations, heFH is much more common, with a prevalence of 1:10 in the Old Order Amish population and 1:67 in South African Ashkenazi Jews [4]. Not surprisingly, among patients with atherosclerotic cardiovascular disease (ASCVD), the prevalence of heFh is 18-fold higher than in the general population [10]. It is estimated that world-wide up to 30 million individuals have heFH, although most studies have been conducted in western populations, leaving estimates of FH in the Eastern Mediterranean region, Asia, and Africa lacking [10].

Diagnosis

Although FH is one of the most common genetic causes of CVD, with an incidence ten times that of sickle cell disease [5], it is underdiagnosed and undertreated [12], with only about 1% of potentially affected patients detected worldwide [10]. Additionally, only one-half of individuals who are diagnosed with FH are adequately treated and a third receive no treated at all [9]. The diagnosis is made difficult by an overlap between the range of LDL-C levels in those with heFH and that of the general population [9]. Only a small fraction (1–5%) of individuals with LDL-C ≥ 190mg/dL have an identifiable FH variant [13]. In contrast, cholesterol screening at 9–11 years of age results in a 0.1% false positive rate [14], making childhood a potentially ideal time to detect FH and creating the opportunity for RCS [15].

There are three internationally recognized criteria for diagnosis of FH [4]: the Dutch Lipid Clinic Network (DLCN) criteria [12], the Simon Boome criteria [16], and the "Make Early Diagnoses to Prevent Early Deaths" (MEDPED) criteria [17]. The DLCN criteria cannot be used in children. Generally, a clinical diagnosis relies on a persistently elevated level of LDL-C, presence of tendinous xanthomas or arcus cornealis, premature CVD, and strong family history of ASCVD. This results in a spectrum of real probability, making definitive diagnosis difficult. Genetic diagnosis relies on identification of a known pathogenic variant in the *LDLR*, *APOB*, *PCSK9*, or *LDLRAP1* genes [12, 17]. Genotyping allows for classification of variants as heterozygous or homozygous, but these terms are complicated by a range in severity of particular variants and the possibility of multiple gene variants. Individuals with homozygous FH (hoFH) have two variant alleles, which are characterized as having no detectable LDLR activity (*receptor negative*) or having reduced LDLR activity (*receptor defective*) [1]. Both disease severity and the level of LDL-C are inversely correlated with LDLR activity level [9]. Depending on which diagnostic criteria is used, different rates of detected variants among individuals classified as definite FH have been reported by retrospective analysis. The DLCN criteria is the most specific with a 63–80% variant rate, the Simon Broome criteria results in 32–61%, while the MEDPED criteria has a reported variant rate of 52–83% [8]. Patients in whom a variant cannot be identified may either have an unknown variant, multiple small effect gene variants

Table 1 Data from Journal of Clinical Lipidology 2016 [27]

Age	Type	Criteria
≥2 years of age	Selective	• 1 or both biologic parents known to have hypercholesterolemia or are receiving LLM*; or • Family history of premature CVD (i.e. men < 55 yrs; women < 65 yrs); or • Whose family history is unknown (e.g. children who were adopted)
≥10 years of age	Universal	• Regardless of general health or the presence/absence of CVD risk factors • If normal, repeat every 5 yrs

**LLM* lipid lowering medication

(polygenic FH), or other conditions (e.g. sitosterolemia or lysosomal acid lipase deficiency) Table 1.

A potential driver of undertreatment is the lack of generalizability of standard risk calculators (such as the European SCORE or the US Framingham Risk Score) in the FH population due to the chronic elevation in LDL-C seen in FH, corresponding to a vastly increased cumulative cholesterol burden and CVD incidence [12]. In the Myocardial Infarction Genetics Consortium CAD case–control cohorts, participants with an identified pathogenic variant in one of the three genes associated with FH were found to be at a significantly higher risk of CAD within each stratum of LDL-C level. For example, when compared to participants with an LDL-C < 130 and no FH variant, odds of CAD were increased 22-fold in individuals with LDL-C ≥ 190mg/dL and an FH variant; however participants with LDL-C ≥ 190mg/dL who did not have an FH variant were only sixfold more likely to have CAD when compared to the same reference group [13]. Thus genetic testing risk is a useful tool for proper risk stratification and clinical decision-making in individuals clinically diagnosed with FH [9].

Prognosis and Treatment

In FH patients, the precursors of atherosclerosis are present from a young age. Children with heFH show increased carotid intimia-media thickness (cIMT) compared to unaffected siblings and may develop aortic lesions by the age of 8–10 years [18]. Increased LDL-C and lowered HDL-C are associated with development of fatty streaks and plaques in children [19]. As atherosclerosis is a major cause of CAD, individuals with FH develop angina and myocardial infarction much earlier than age matched peers. Untreated, individuals with heFH often develop CHD by 55–60 years-of-age, while those with hoFH become symptomatic by age 12, with death usually occurring before 20 years-of-age [12]. Outcomes are affected by the wide range of LDL-C seen in FH patients, as well as standard risk factors such as diabetes, diet, exercise, Lp(a) level, and HDL-C level. Lp(a) levels are elevated in 30% of those with FH compared to the general population, although the mechanism remains unclear [20]. Treatment of FH with conventional lipid lowering therapy is generally very effective in individuals with receptor defective forms of the disease while those with null receptor variants have decreased response [1]. Consensus guidelines recommend statin therapy for children with severe LDL-C elevations beginning at the age of 8 to 10 years, although an earlier age may be considered in hoFH patients [18]. Treatment goals for LDL-C are < 130mg/dL or a reduction of ≥ 50% from baseline [19].

Because early identification and treatment of FH can increase life expectancy by decades [5, 21], global underdiagnosis results in millions of individuals developing premature CVD, increasing healthcare costs and utilization. It has been well demonstrated that early detection of FH allows for early intervention, thus reducing the LDL-C associated CVD risk in adults and children with heFH to levels close to that of the general population. Using data from Huijgen et al. [21] and Starr et al. [22], Nordestgaard et al. offered the following sobering observation: "*The cumulative LDL-C burden of a 55-year-old person without FH is typically 160 mmol, a burden sufficient for CHD to develop. For an individual with heterozygous FH, this LDL-C burden is reached by age 35 if untreated, by age 48 if treated since age 18, and by age 53 if treated since age 10. An untreated subject with homozygous FH will reach this level at age 12.5*." [12]

This, as well as the opportunity for RCS of family members, provides a clear rationale for the identification and treatment of FH in childhood [23, 24].

Overview of Reverse Cascade Screening

Method

Reverse cascade screening involves testing first-degree relatives of youth with clinical or genetically confirmed FH, utilizing biochemical and/or genetic testing (if a causative gene is identified in the index case).

The figure below illustrates how RCS is performed, providing highly efficient and cost-effective testing. In contrast to traditional cascade screening, which relies on identification of FH in an adult and is often performed after an ASCVD-related event, RCS relies on identification of FH in youth through universal or selective cholesterol screening. Thus, RCS provides the opportunity to identify and treat affected individuals at a younger age, ideally prior to the onset of symptoms Fig. 1.

UCS during childhood accompanied by RCS is currently recommended by the International Atherosclerosis Society (IAS) [26], the National Lipid Association (NLA) [27], and the National Heart, Lung, and Blood Institute (NHLBI) [14]. Screening guidelines are shown in the table.

Children rarely develop the classic physical features of FH such as corneal arcus and xanthoma, and are generally asymptomatic [28]. While UCS is recommended by all major medical societies and organizations, surveys report only 30% of pediatricians in the US routinely screen children 9–11 years-of-age [29, 30]. A retrospective analysis of 400,000 US children aged 11–17 reported that only 37% of the population received cholesterol screening, and found a strong association between obesity and screening rate, but not FH incidence [31]. It should be noted that adult cut-offs for an abnormal LDL-C would miss 28–75% of children with FH [28]. In youth, FH is defined as a persistently elevated LDL-C level of ≥ 160mg/dL,

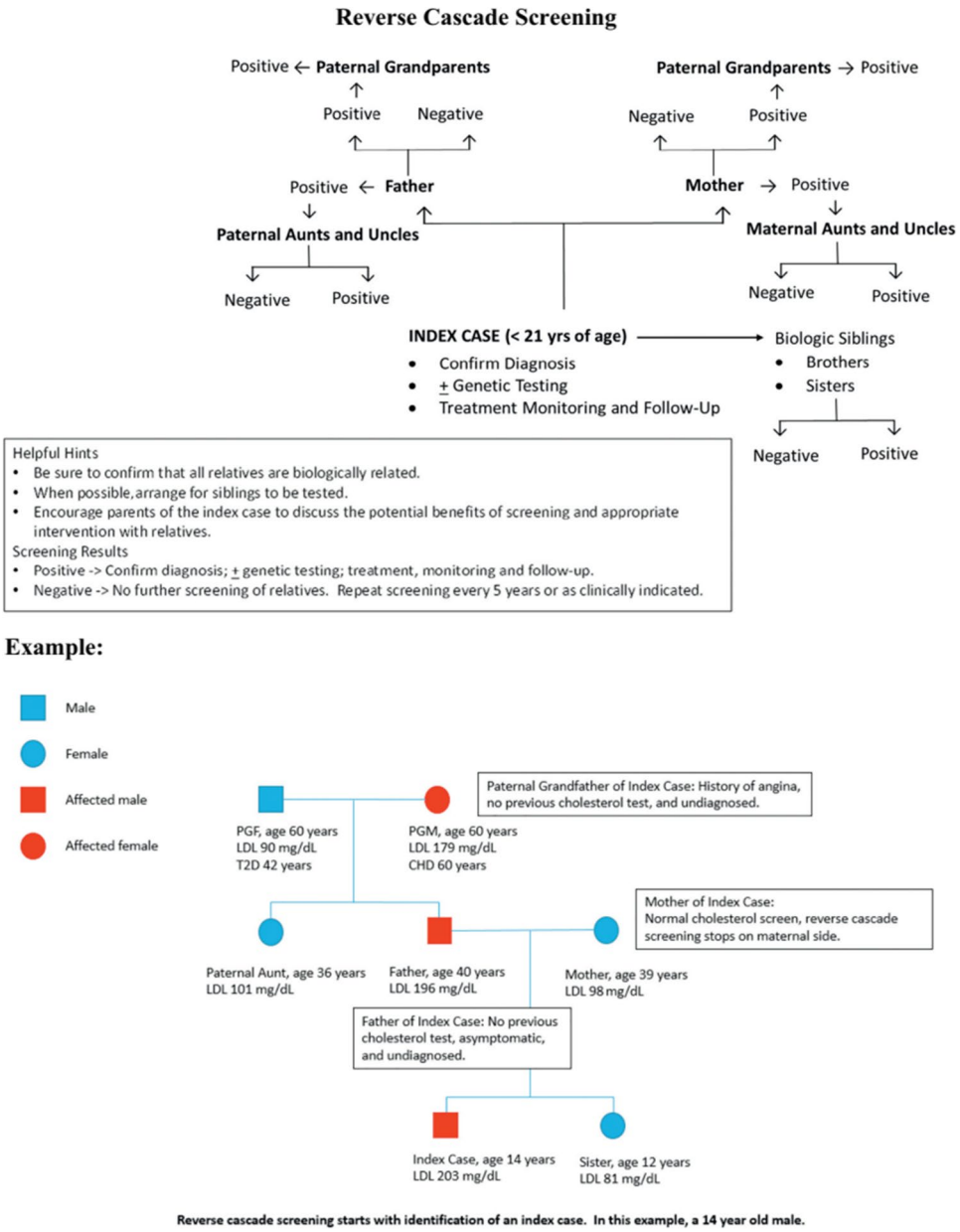

Fig. 1 Example of Reverse Cascade Screening Technique. Used with permission from Vinson 2019 [25]

rather than ≥ 190mg/dL, especially in those with a first degree relative who has a history of hypercholesterolemia, premature CAD, or a confirmed pathogenic variant [18].

Despite the obvious benefits and widespread support, there remains a lack of coordinated UCS and RCS in the US [32]. Three European countries have conducted biochemical FH RCS pilot programs on an institutional or regional level, while 19 more have programs involving genetic RCS [33]. Of the > 60 countries participating in the European Atherosclerosis Society Familial Hypercholesterolemia Studies Collaboration, about one third offer regional genetic-based cascade screening [34]. Cascade screening may present challenges for the typical healthcare system, evidenced by a 76% reduction in number of diagnoses made in the Netherlands two years after the 2013 termination of a nationally funded program in the Netherlands [35••].

Cost-Effectiveness, Accuracy, and Benefit

The cost-effectiveness of screening depends on the FH prevalence in the target population, cost of testing, the false-positive rate and costs associated with evaluating potential cases, treatment of positive cases and expected savings from the prevention of ASCVD-related events and premature death. For a screening program to be considered cost-effective it is often compared to national cost-effectiveness thresholds [36]. In the US, the value of $50,000–100,000 USD per quality-adjusted life year (QALY) is commonly used [36,

37]. A full discussion of each of each of these factors is beyond the scope of this review, however, several observations have been made.

The value of cholesterol screening decreases as an individual ages. Because LDL-C levels tend to increase with age, the overlap between the LDL-C levels in FH and those who are unaffected increases. By adulthood, only 1–5% of those with LDL-C ≥ 190mg/dL are found to have an FH variant [13]. In contrast, screening children at the age of 9–11 results in a false positive rate of 0.1% [14]. Thus, the process of identification and diagnosis is simplified in youth compared to adults. Additionally, detection of an index case at a young age creates an opportunity to identify affected siblings and young parents prior to clinical symptoms, avoiding ASCVD-related events and restoration of a normal life expectancy [23]. With a prevalence of 1:311 in the general public, a false positive rate of 0.1% would result in approximately one false positive case for every three FH positive patients screened. While less specific, LDL-C screening is less expensive than genetic testing for FH.

Treatment of cardiovascular disease accounted for 12% of total US health expenditures in 2019 and 2020 ($422.3 billion), more than any other major diagnostic group [38]. Although individuals found to have an elevated LDL-C may not meet criteria for the diagnosis of FH, most will benefit from treatment. Thus cholesterol screening benefits even those with "false positive" results. Primary prevention of CVD is far less expensive than the treatment of major adverse cardiovascular events (MACE). Estimating the actual cost savings per patient treated or screened is difficult, as described in the 2011 AHA policy statement, "Value of Primordial and Primary Prevention in CVD". *"Assessing the value of prevention in apparently healthy patients is generally more difficult than evaluating therapy for established disease because the time horizon to the clinical manifestation of disease is generally long—many decades in the young. Thus, it is difficult, perhaps impossible, to assess long-term effectiveness in terms of survival or quality-adjusted life-years (QALYs) or associated costs because of increasing uncertainty about outcome the further one tries to look into the future."* Nonetheless, with current treatment guidelines, statins are felt to be cost-effective at a $50,000 willingness-to-pay threshold up to $2.21 per pill [39].

Identification of FH at an early age may also reduce the disparity reported in the treatment of males versus females. A recent cross-sectional study of children enrolled in the FH collaboration registry found that among those ~ 9 years-of-age, males and females received similar treatment with lipid lowering medication, in contrast to adult females who received less aggressive treatment than adult males [28, 40].

Early diagnosis of FH provides the additional benefit of lifelong inclusion in national or international registries, allowing for systematic and standardized data collection and processing, to help inform guidelines and future recommendations for standard of care [41].

Legal and Ethical Concerns

Ethical and legal challenges represent potential barriers to effective and timely RCS. Despite the increased risk of premature morbidity and mortality in individuals with FH, in the absence of an established relationship, direct contact of a relative by a healthcare professional is prohibited by HIPPA. Parents may be provided a letter, detailing the condition, risks, treatment options, and benefits of early diagnosis and be encouraged to share it with other family members. However, this approach has proven to be less effective and efficient. A comprehensive program to facilitate RCS, utilizing a third-party contact, has recently been developed in an attempt to improve and simplify this process [42•].

Conclusion

Traditional approaches to cholesterol screening have had limited impact on identification of individuals with FH, particularly at an early age. UCS during childhood with reflex RCS offers at least three unique benefits: 1) an opportunity to identify most if not all individuals with FH, ideally prior to clinical symptoms/ events related to ASCVD; 2) identification of affected relatives, many of whom have never been tested nor diagnosed; and 3) an opportunity for earlier intervention, improving outcomes and reducing healthcare cost to the individual and society. Challenges include the lack of a centralized program and a prohibition banding direct contact of extended family members of the index case. Despite strong support for UCS and RCS, screening rates remain low throughout the U.S. and the world. Future research is needed to identify barriers and ways of improving cholesterol screening.

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Declarations

Competing interests The authors declare no competing interests.

Conflicts of Interest None to report.

Human and Animal Rights and Informed Consent No animal or human subjects were used in this study.

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- •• Of major importance

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