Journal of Pediatric Nursing 44 (2019) 50–55

Contents lists available at ScienceDirect

Journal of Pediatric Nursing

Reverse Cascade Screening for Familial Hypercholesterolemia

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ARTICLE INFO

Article history:
Received 27 March 2018
Revised 16 August 2018
Accepted 20 September 2018

Keywords:
Reverse cascade screening
Cholesterol
Familial hypercholesterolemia
Children

ABSTRACT

Problem: Cardiovascular disease (CVD) is the leading cause of death in the U.S. and in most Western countries. Early identification and treatment of individuals with elevated levels of atherogenic cholesterol, a major contributor to CVD, have been shown to be effective and safe in reducing premature morbidity and mortality, especially in familial hypercholesterolemia (FH). Cholesterol screening of youth also provides a unique means of identifying affected family members through reverse cascade screening (RCS).
Eligibility Criteria: A PubMed review of all relevant articles from 2000 to 2016 was conducted of familial hypercholesterolemia and cholesterol screening of youth.
Results: We provide an overview of cholesterol screening, outline the role of the pediatric nurse in the lipid clinic, and discuss effectiveness and potential barriers, including cost and confidentiality considerations of RCS.
Conclusions: Early identification and effective intervention of youth with FH, including adoption of a heart-healthy lifestyle, has the potential of 1) markedly reducing or eliminating atherosclerotic cardiovascular disease and related events in future generations and 2) provides a unique means of identifying affected family members.
Implications: Pediatric nurses play a vital role in the education and care coordination of children diagnosed with FH and screening of relatives. Identification of a child with FH with effective screening of relatives combines the benefits of universal and cascade screening, and has the potential of detecting all living cases of FH. While potentially providing significant benefit to those at risk for premature CVD, a RCS program needs to carefully consider ethical, psychological, and financial implications as well.

Published by Elsevier Inc.

Introduction

In 2011, the NHLBI Expert Panel published recommendations for universal cholesterol screening of all youth 9–11 years of age, with repeat screening at 17–20 years of age if normal (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, 2011). The primary goal of cholesterol screening is to identify youth with familial hypercholesterolemia (FH), a genetic disorder associated with life-long elevation of cholesterol and a dramatic increase in risk of premature coronary heart disease (CHD) after 20 years of age. Early identification and effective intervention of youth with FH, including adoption of a heart-healthy lifestyle, has the potential of markedly reducing or eliminating atherosclerotic cardiovascular disease (ASCVD) and ASCVD-related events in future generations.

Cholesterol screening of youth also provides a unique means of identifying affected family members. Because most mutations that cause FH are autosomal dominant, identification of affected youth creates a unique opportunity of identifying relatives with FH through reverse cascade screening (RCS) (Jacobson et al., 2015). Given the growing number of lipid clinics throughout the U.S. focused on the needs of children and adolescents (Hamilton, Gidding, Wilson, 2017), pediatric nurses play a key role in RCS. To better understand the methods utilized, prior to implementing a RCS program in our pediatric lipid clinic, we undertook a PubMed review of all relevant articles from 2000 to 2016. In this article, we provide an overview of cholesterol screening, outline the role of the pediatric nurse in the lipid clinic, and discuss effectiveness and potential barriers, including cost and confidentiality considerations of RCS.

Overview of Familial Hypercholesterolemia

Abnormal cholesterol levels are commonly caused by genetic mutations in lipid and lipoprotein metabolism, acquired conditions (e.g., high fat, high carbohydrate diet, lack of exercise, obesity, and a variety of medications), or both. Although lifestyle related dyslipidemias are common, genetic mutations that alter regulatory mechanisms of lipid and lipoprotein metabolism, such as FH, pose a unique concern. Because elevated cholesterol is present from birth, FH results in lifelong elevation of LDL-C, significantly increasing the risk of premature cardiovascular disease in adulthood (Gidding et al., 2015; Goldberg et al., 2011).

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https://doi.org/10.1016/j.pedn.2018.09.011
0882-5963/Published by Elsevier Inc.

Table 1
LDL-C diagnostic categories.

Category	Description	Minimum LDL-C, mg/dL		
		Age < 20 y	Age 20–29 y	Age 30+ y
1	General population 95th percentile	130	160	190
2	80% have FH in first-degree relatives[a]	150	170	200
3	80% have FH in general population[b]	190	220	260
4	99% have FH in general population	220	240	280
5	99.9% have FH in general population	240	260	300

Hopkins, Toth, Ballantyne, & Rader, 2011
[a] Used for cascade screening.
[b] Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, 2011.

Although FH is very common (1 in 250), <1% of those with FH are identified in the U.S. and much of the world (Nordestgaard et al., 2013). The condition is most frequently inherited in an autosomal dominant pattern, resulting in lack of or reduced removal of LDL particles from the plasma. Individuals with heterozygous FH are at 3- to 4-fold higher risk for developing CHD, which typically occurs 10 years earlier than in unaffected individuals. Homozygous (HoFH) and recessive types of FH occur but are rare (~1:1000,000). Recent publications, however, suggest the prevalence of HoFH may be more frequent than previously reported (Cuchel et al., 2014).

Although universal screening of all children starting at age 9–11 is currently recommended in the U.S. (Committee on Practice and Ambulatory Medicine, 2017), the literature suggests that high levels of LDL-C can be accurately detected in much younger children (Wald et al., 2016). Diagnostic thresholds of LDL-C likely vary by age (Table 1). Levels of both total and LDL-C show considerable overlap between adults with and without FH, making detection through screening more effective in children. Detection at a young age offers opportunity for early intervention of the child and affected relatives through RCS.

Traditional cascade screening starts with identification of an affected individual, usually a symptomatic adult, who commonly is experiencing angina, or who has suffered a fatal or non-fatal myocardial infarction. Rather than wait for symptoms and events to identify an individual with FH, RCS usually starts with identifying an asymptomatic child, frequently through universal screening as recommended by a majority of national organizations and professional societies, including the NHLBI, National Lipid Association (NLA), American Academy of Pediatrics (AAP), and the American Heart Association (AHA). RCS involves systematic testing of all 1st-degree relatives (parents, siblings, and children) of the index case, followed by testing of 2nd- and 3rd-degree relatives if any of the 1st-degree relatives are affected. (Fig. 1). Often, adult relatives may not have been tested and can be identified and effectively treated before becoming symptomatic and/or having a CVD-related event. Because of the dominant inheritance of hypercholesterolemia, the benefits of a RCS program are likely to extend beyond the affected youth to relatives across multiple generations. Identifying all at-risk individuals is critical in preventing premature morbidity and mortality due to CVD.

Cholesterol Screening in Children and Adolescents

Several screening strategies have been proposed to identify individuals with elevated LDL-C who are at high risk for premature CVD. These include targeted screening of individuals based upon family history and/or known CVD risk factors, universal screening, cascade and reverse cascade screening of relatives of individuals found with either early CVD or LDL-C consistent with FH, and big data approaches to identify persons with high cholesterol and risk of premature CVD (Pyles, Elliott, & Neal, 2017). Because affected children are asymptomatic, often of normal weight, and the family history is either unavailable, incomplete, or unreliable, systematic universal screening is recommended in the U.S. to facilitate early identification of children and adolescents with hypercholesterolemia. A summary of current recommendations by the NHLBI, NLA, and ACC/AHA is shown in Table 2.

What to Order

For both the index case and RCS of relatives, the most practical approach to screening is biochemical testing of cholesterol, which is inexpensive, reliable, and readily available. Either a fasting or non-fasting lipid profile is acceptable. Blood samples can be drawn by venipuncture or finger stick. If available, point of care lipid testing (e.g., table-top analyzer) has proven reliable and correlates well with standard laboratory results. Adults who participate in RCS should be encouraged to seek advice from their primary care provider regarding cholesterol testing, interpretation, and treatment, if needed. Since some adults may not have medical insurance, it is important to help identify testing sites that can provide low cost, reliable testing and counseling.

Cost Effectiveness

Although capable of identifying asymptomatic individuals with hypercholesterolemia, the cost effectiveness of universal screening has not yet been determined (Besseling, Sjouke, & Kastelein, 2015). Cascade screening is more cost effective than any other screening strategy currently available. However, cost of genetic testing has dramatically decreased in recent years, and may become more acceptable and feasible in the future.

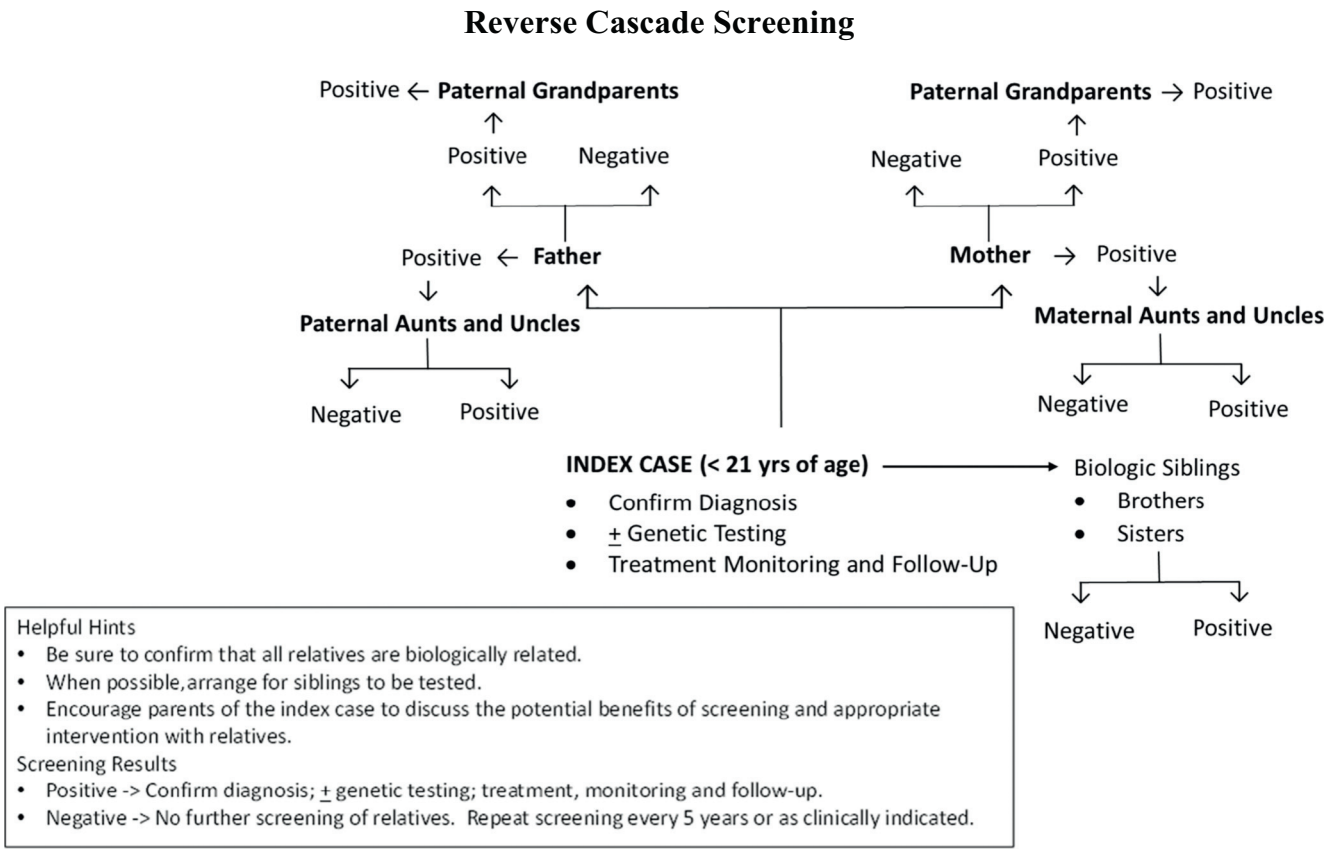
Ademi and colleagues conducted a systematic review to evaluate the cost-effectiveness of screening and treatment of FH. The authors concluded that although cascade screening for new cases of FH appears to be cost-effective, the conclusions were method specific, and dependent upon the underlying prevalence of FH, validity of the screening tests, and use of different approaches to assess the outcomes of treatment (Ademi, Watts, Juniper, & Liew, 2013).

Results of various screening methods, including the identification and treatment of patients with FH by universal screening, opportunistic screening in primary care, screening of people admitted to hospital with premature myocardial infarction, or tracing family members of affected patients was reported by Marks and colleagues. These authors found screening family members of people with FH to be the most cost effective option for detecting cases across the whole population (Marks, 2002).

Diagnostic Accuracy of Cascade Screening

In general, screening relies upon biochemical testing of cholesterol, genetic testing, or a combination of both.

The NHLBI recommends routine universal screening starting at 9–11 years of age, prior to puberty-related changes in cholesterol. To determine the optimum age for screening, Wald and colleagues investigated the accuracy of cholesterol screening in children, starting at birth (Wald, Bestwick, & Wald, 2007). Although newborn screening would offer a convenient and inexpensive means of cholesterol screening, it was not found to be reliable at this young age. In contrast to the recommendations published by the NHLBI, the best age range for screening appears to be between 1 and 9 years, as determined by optimal discrimination using cholesterol measurement between children with and without FH. At a false positive rate of 0.1%, the detection rates in the 1–9 year age group were 88% and 85%, for total cholesterol and LDL-C, respectively. Cholesterol screening can be easily incorporated into scheduled health maintenance visits (e.g., 2 year well-child check),



Example:

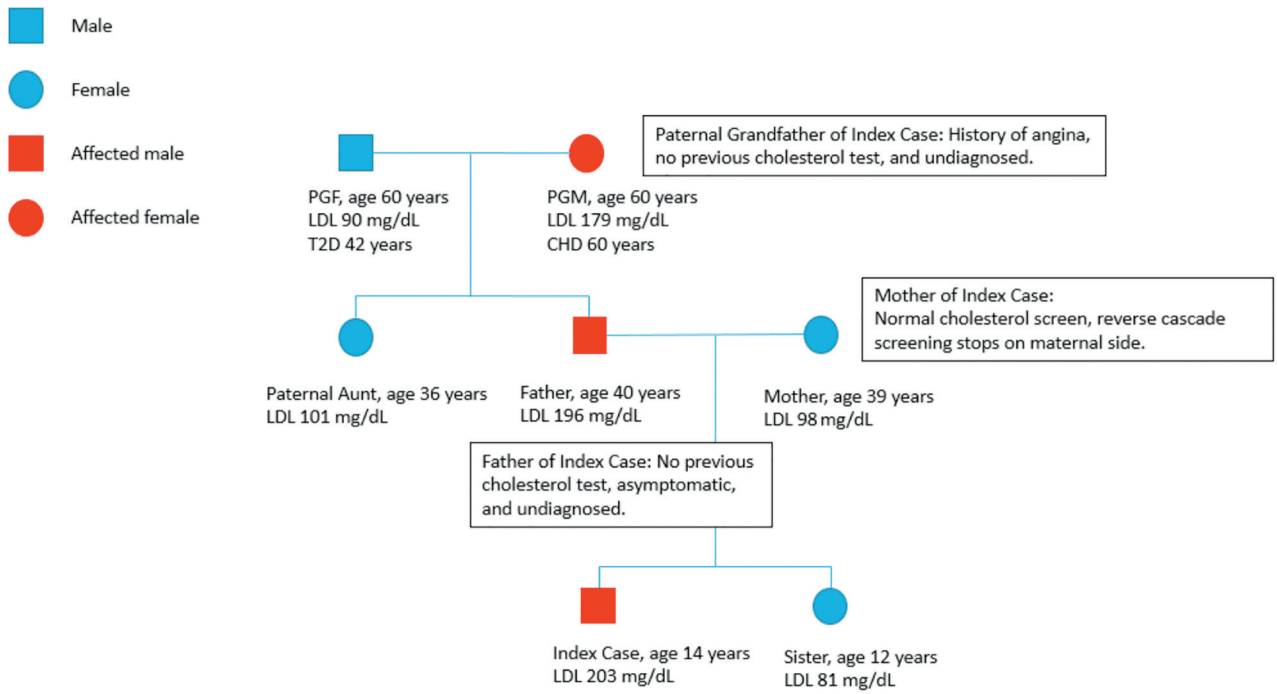


Fig. 1. Reverse cascade screening schematic and example.

Table 2
Cholesterol screening guidelines.

	NHLBI[a]	NLA	ACC/AHA
Who to screen?			
Selective screening	Yes	Yes	Yes
Universal screening	Yes	Yes	Yes
Age at first screening?			
Selective screening	≥2 yrs	≥20 yrs	≥20 yrs
Universal screening	9–11 yrs	≥20 yrs	≥20 yrs
Repeat screening[b]	17–20 yrs	Every 5 yrs[c]	–
What to order?			
Fasting or non-fasting lipid panel	Yes	Yes	Yes
Calculate non HDL-C	Yes	Yes	Yes
Risk factors assessment?	Yes	Yes	Yes
ASCVD risk 10 year estimate?	N/A[d]	Yes[d]	Yes[d]

NLA = National Lipid Association (Jacobson et al., 2014; Jacobson et al., 2015). ACC/AHA = American College of Cardiology/American Heart Association (Stone et al., 2014). NHLBI = National Heart, Lung, and Blood Institute (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, 2011).

[a] These recommendations have been endorsed by the American Academy Pediatrics, National lipid Association, and American Heart Association.

[b] If initial levels of atherogenic cholesterol (non-HDL-C and LDL-C) are in the desirable range.

[c] Or sooner based upon clinical judgment.

[d] Risk calculators are not applicable to children and adolescents, and may either over- or under estimate risk in those <40 years of age.

negating the need for additional clinic visits and blood testing, and has been shown to be acceptable to parents.

The majority of genetic causes of FH include mutations of the LDL receptor gene (*LDLR*), with <5% caused by gene mutations of apolipoprotein B (*APOB*) and proprotein convertase subtilisin/kexin type 9 (*PCSK9*). Over 1000 mutations of the LDLR have been identified. In individuals with a clinical diagnosis consistent with FH, 70–80% have been shown to have a causative mutation, while in 20–30%, the diagnosis is less certain (Varret, Abifadel, Rabes, & Boileau, 2008). Because FH may be caused by a mutation other than those involving LDLR, APOB, or PCSK9, a mutation may not be detected by current testing methods in 20–40% of those screened (Brautbar et al., 2015). Therefore, prior to genetic testing, the individual should be informed that genetic testing is not 100% sensitive. However, the inability to identify a genetic cause does not exclude a diagnosis of FH, and individuals with a clinical diagnosis of FH alone may still benefit from lipid-lowering therapy (DeMott et al., 2008).

While the results of initial cholesterol screening help to identify individuals who are likely to have FH, confirmation of the diagnosis is needed to help determine the most appropriate treatment. Although there are published criteria for diagnosing FH (Goldberg et al., 2011), in the U.S., most adults and children are diagnosed clinically (Ahmad et al., 2016; De Ferranti et al., 2017).

Dietary Management

In those suspected to have FH, repeat cholesterol testing should be obtained in 3–6 months, ideally after implementation of therapeutic lifestyle changes that includes a diet with 25–30% of calories from fat, ≤7% from saturated fat, ~10% from monounsaturated fat; <200 mg/day of cholesterol; while avoiding trans-fats as much as possible. Family history, when available and reliable, repeat cholesterol testing, exclusion of secondary causes, and clinical judgement are all helpful in determining the likely cause of the elevated cholesterol. Since those with LDL-C levels > 190 mg/dL are at significant risk for premature CHD, in addition to recommendations for a healthy lifestyle, treatment with a lipid-lowering medication is recommended beginning at 8 years of age and older (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, 2011).

Diet modification and other lifestyle interventions have been shown to be modestly effective in lowering LDL-C in children and adolescents. A diet that has a total fat content of 25–30% of calories, saturated fat content of ≤7% of calories and dietary cholesterol < 200 mg/day is beneficial in lowering LDL-C and non-HDL. This diet has no adverse effects, including no adverse effects on growth and development (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, 2011). Genetic confirmation of the diagnosis, while helpful, is not necessary for treatment since individuals with FH who have unidentifiable mutations are at high risk (Brautbar et al., 2015).

Those with mild-to-moderate elevation of LDL-C (130–189 mg/dL) should be encouraged to undergo therapeutic lifestyle changes. If levels remain elevated after 6 months, appropriate treatment, including use of lipid-lowering medications, should be considered. Given the evidence linking hypercholesterolemia to premature ASCVD, lipid-altering pharmacotherapy should be considered in children, adolescents, and young adults at moderate to high risk of premature ASCVD, especially those with FH.

Lipid Lowering Medications

In children 10 years of age or older, statins are the drug of choice for LDL-C lowering, but may be considered at a younger age based upon additional CVD risk factors and family history. This recommendation has been endorsed by the National Lipid Association, American Heart Association, and the Academy of Pediatrics. The decision to implement LDL lowering therapy in this young age group is based upon clinical judgement after careful review of ASCVD risk factors, current medications, and medical conditions, potential benefits, as well as short-and-longer-term side effects of treatment. All commercially available statins, except pitavastatin, are approved by the FDA for use in children with FH when the LDL-C level is >190 mg/dL or >160 mg/dL with 1 or more risk factors (Bays, Jones, Orringer, Brown, & Jacobson, 2015). Although available evidence focuses on relatively short-term use of statins, results of clinical trials support the safety and efficacy of pharmacologic treatment to lower atherogenic cholesterol in children age 10 and above (Wiegman et al., 2004).

Randomized clinical trials of children and adolescents with FH treated with lipid-lowering therapy demonstrated LDL-C reductions similar to those in adults. No serious adverse events were reported, and following treatment, surrogate markers of atherosclerosis, such as carotid-intima-media thickness were found to be comparable to that of unaffected siblings. While meta-analysis of randomized controlled trials in children with FH have shown no adverse events on growth, development, or sexual maturation with use of a statin, there is need to remain vigilant in regards to long-term outcomes, safety, and cost effectiveness.

Ethical Issues

Current practices in the U.S. allow sharing most of a youth's medical findings and recommendations with the biologic parent or legal guardian. Furthermore, biologic parents are generally asked to give a detailed family history, including their own personal history, of other family members who are known to have hypercholesterolemia, those who are receiving lipid lowering medications, and whether there is a family history of ASCVD-related symptoms or events, included premature death. Parents may also consent to allow a copy of their own pertinent medical history, including diagnostic test results and treatment, to be sent to the child's healthcare provider. Such an approach, which often helps to validate the parent's personal history, raises important ethical concerns and issues of confidentiality.

Directly contacting a child's relatives, as practiced in the Netherlands (Newson & Humphries, 2005; Umans-Eckenhausen, Defesche, Sijbrands, Scheerder, & Kastelein, 2001), is problematic in the U.S. and raises

important confidentiality concerns. Although relatives of an FH proband are at increased risk of having FH and the potential for premature CVD, direct contact by the healthcare provider, including the Lipid Clinic Nurse, would be considered unethical by many.

Currently in the U.S., it is not possible for the child's healthcare providers to directly contact 2nd and 3rd degree relatives, although such an approach is likely to be more informative, accurate, and efficient. As an alternative, parents can be given a detailed letter describing the health risks associated with FH, the pros and cons of screening, including potential psychologic and insurance issues, and the benefits of effective treatment to lower cholesterol. Parents should be encouraged to contact their relatives in a timely fashion with appropriate information. In our clinic, additional information is given to the parents that includes a list of local resources for web-based information and low cost screening. All relatives are encouraged to talk with their personal healthcare providers for more information, to address concerns, and provide individual guidance.

Psychologic Issues

While relatives of an individual with FH usually believe that cholesterol screening is beneficial (Newson & Humphries, 2005), awareness of the need for testing, and acceptance of potentially having a genetic condition which left untreated could result in ASCVD, may result in anxiety, anger, and fear. Although acknowledging their potential vulnerability and risk, some may choose not to be tested, giving way to "fatalism," a belief that all events are predetermined and therefore inevitable. While 10% of individuals found to have familial hypercholesterolemia have been reported to have anxiety related to the diagnosis, the results were no higher than would be expected in the general population (Andersen, Jensen, Juul, & Faergeman, 1997). Furthermore, in the Netherlands, cascade screening was considered acceptable to the vast majority, quality of life was unaffected, and resulted in an increase in treatment and adherence (van Maarle, Stouthard, Marang-van de Mheen, Klazinga, & Bonsel, 2001). Published data suggests that the psychologic impact of genetic testing for FH is frequently perceived by those tested to be more accurate and have greater accuracy (Andersen et al., 1997).

Financial Issues

The ever changing criteria for insurance coverage, including pre-existing conditions, and variable costs, pose valid concerns. The potential of misuse to deny insurance coverage or increase premiums has led to a moratorium of genetic testing in Europe (Morrison, 2005).

Lipid clinics planning to implement a RCS program for FH should also carefully consider the infrastructure costs of doing so. In addition to personnel, additional costs may include data collection and tracking, counseling, informational inquiries, and a potential increase in demand for clinical services. In some cases, discussions with and coordination of care with adult healthcare providers may also be necessary, especially for adult relatives and transitional care of older adolescents.

Role of the Pediatric Nurse in Cascade Screening

Nurses play a key role in the pediatric lipid clinic. Responsibilities include helping the child and family understand test results, the disease process, and implications for health, discussing educational opportunities, including informative websites such as those provided by the NLA – http://www.learnyourlipids.com/ – and Familial Hypercholesterolemia Foundation – https://thefhfoundation.org/ – and assisting the family in adaptation to the medical, psychological, and familial implications of a genetic condition. In addition, the pediatric nurse is often able to recommend dietary, psychologic, and genetic counseling as needed. When these services are utilized, the nurse is able to reinforce the intervention strategies to help the child and family achieve success.

Other roles include collection of a detailed family history with special emphasis on family members: a) with known CVD risk factors (elevated cholesterol, xanthoma, etc.); b) who have undergone a procedure (stents, CABG); and c) who may have experienced a premature event (MI, stroke); d) describe the pros and cons of and the process by which RCS is appropriately conducted; and e) provide talking points for the family to share with others, including family members. The latter may be facilitated by examples of "family letters" intended to be shared with at-risk family members.

Conclusions

Pediatric nurses play a vital role in the education and care coordination of children diagnosed with FH and screening of at risk relatives. Identification of a child with FH with effective screening of 1st, 2nd, and 3rd-degree relatives combines the benefits of universal and cascade screening, and has the potential of detecting all living cases of FH. Early recognition of a child or young adult with FH, coupled with therapy from a young age, will impede, if not arrest, the onset of atherosclerosis. While potentially providing significant benefit to those at risk for premature CVD, a RCS program needs to carefully consider ethical, psychological, and financial implications as well. Outcome measures and additional research are needed to help improve identification of individuals at high risk of cardiovascular disease and which create opportunities for early health education, adoption of healthy lifestyles, and appropriate interventions.

Acknowledgments

The authors would like to acknowledge Dena Hanson and Ashley Brock for their assistance in preparing and editing this manuscript.

Author statement

All authors were involved in the preparation, writing, and editing of this manuscript.

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