There is clear pathologic evidence that the process of atherosclerotic cardiovascular disease (CVD) begins in childhood with the deposition of fatty streaks within the arterial walls and subsequently progresses into fibrous plaques throughout adolescence and early adulthood. This evidence has generated a substantial interest outside of primary and secondary CVD prevention and a focus toward primordial prevention. The recent National Heart, Lung, and Blood Institute (NHLBI) Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents updated recommendations for the identification, management, and treatment of all major cardiovascular risk factors in pediatrics (1). These guidelines, which have also been endorsed by the American Academy of Pediatrics (AAP), address issues related to nutrition, physical activity, tobacco, high blood pressure, lipids, obesity, and the metabolic syndrome. One major challenge of this integrated approach is accounting for the fact that the manifestation of CVD typically occurs later in life and a variety of environmental factors influence the progression or attenuation of risk. One updated NHLBI recommendation that is likely to cause controversy is the recommendation of universal screening for dyslipidemia by the age of 9–11 years and subsequently at an age of 17–21 years. Lipid screening should be performed with either a fasting lipid panel [total cholesterol, HDL cholesterol (HDL-C), triglycerides, non–HDL-C, LDL cholesterol (LDL-C)] or a nonfasting lipid panel (total cholesterol, HDL-C, non–HDL-C).

Clinical Practice Guidelines: Historically Conflicting and Controversial

Initiatives and research emerging over the past 2 decades have led to a variety of approaches and attitudes toward screening for pediatric dyslipidemias, which have produced conflicting recommendations and variations in clinical practice. In 1992, the National Cholesterol Education Program first recommended a tiered approach to pediatric lipid screening, in which a fasting lipid profile was recommended if the child had a positive family history of premature CVD or dyslipidemia, had an unknown family history, or presented with other risk factors, such as hypertension, obesity, or diabetes. Although the American Heart Association recommended a similar approach in 2007, the US Preventive Services Task Force simultaneously concluded that the evidence was insufficient to recommend screening for dyslipidemia in infants, children, adolescents, or young adults. One year later, the AAP released an updated policy recommending a targeted approach to screening between the ages of 2 and 10 years with a fasting lipid profile in children with a family history of premature CVD, dyslipidemia, or the presence of other high-risk factors. Further inconsistency among experts came with the National Lipid Association publication in 2011, which recommended universal screening over targeted screening in children between the ages of 9 and 11 years by means of either a fasting lipid profile or a nonfasting lipid profile that included non–HDL-C. What was a family practitioner, pediatrician, nurse, nurse practitioner, or physician assistant supposed to do in the face of all this conflicting information?

Reasons to Screen for Dyslipidemias

To understand why there is such conflicting information in the guidelines, it is relevant to discuss the purpose of lipid screening in children and the types of abnormalities that will inevitably be encountered, depending on the screening approach used. Historically, lipid screening in pediatrics focused on the identification of genetic hyperlipidemias, primarily familial hypercholesterolemia (FH), which causes severely increased blood cholesterol concentrations and arises from defects in the LDLR (1) (low density lipoprotein receptor), APOB [apolipoprotein B (including Ag(x) antigen)]

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2 Nonstandard abbreviations: CVD, cardiovascular disease; NHLBI, National Heart, Lung, and Blood Institute; AAP, American Academy of Pediatrics; HDL-C, LDL cholesterol; LDL-C, HDL cholesterol; FH, familial hypercholesterolemia; CARDIAC, Coronary Artery Risk Detection in Appalachian Communities (project).

3 Human genes: LDLR, low density lipoprotein receptor; APOB, apolipoprotein B (including Ag(x) antigen); PCSK9, proprotein convertase subtilisin/kexin type 9.
Dyslipidemia is tightly linked to, although not causative of, diseases such as obesity and type 2 diabetes. The prevalence of these diseases has markedly increased in the US, and the use of lipid screening may identify children at increased risk for early atherosclerosis, diabetes, CVD, and other comorbidities in adulthood. An estimated 170 million individuals in the US are overweight or obese, equating to 67% of adults and 32% of children, with prediction models estimating a 15% increase in adult coronary heart disease over the next 2 decades and >100 000 excess cases being the direct result of childhood obesity (2). Surveillance of lipids and lipoproteins from childhood to adulthood is an area of relevance, not only for primary prevention but also for the development of innovative primordial prevention strategies. Furthermore, there is evidence that the cardiovascular risk attributable to childhood obesity may be reversed and attenuated if the obesity is treated through lifestyle intervention or modifications (3). It is also important that the potential educational benefits of lipid screening in obese children and adolescents not be overlooked. The concept of present-day actions on future health outcomes is a difficult one for children to grasp. It is hypothesized that documenting the presence of dyslipidemia could reinforce the educational and interventional efforts for the individual and the family.

A Change to Universal Screening

The NHLBI universal-screening recommendation stems from evidence that the previous high-risk screening strategies were largely ineffective and failed to identify up to 60% of children and adolescents with hypercholesterolemia (1). Particular difficulty was noted for the children with younger parents who themselves did not manifest signs of CVD or were unaware of their own lipid profiles. Furthermore, there was a low physician adherence to the seemingly complicated and conflicting screening recommendations and limited compliance from the children and families once dyslipidemia was identified. The CARDIAC (Coronary Artery Risk Detection in Appalachian Communities) Project evaluated the effectiveness of screening based on family history alone in 20 266 fifth graders and demonstrated that a majority (71.4%) met the criteria for screening based on family history alone (4). Of these children, 1204 (8.3%) had an LDL-C >130 mg/dL (>3.37 mmol/L), and 170 (1.2%) had an LDL-C >160 mg/dL (>4.14 mmol/L). Of the individuals who would not have met screening guidelines but still underwent testing as part of the study, 548 (9.5%) had an LDL-C >130 mg/dL (>3.37 mmol/L), and 98 (1.7%) had an LDL-C >160 mg/dL (>4.14 mmol/L), thereby demonstrating that the targeted screening approach was largely ineffective in identifying children in need of intervention from family history alone. The link between inadequate screening early in life and future adverse CVD events, however, is a complex issue that needs to be addressed with outcome studies. It is evident that the overall number of children who qualify for screening with the previous strategies has increased substantially over the years. The reasons for the ineffectiveness of the high-risk approach are largely complex with many socioeconomic facets but have ultimately led to the recommendation of universal screening.

Treatment Modalities

With the presence of hyperlipidemia, one must consider the potential need for pharmacologic treatment, an issue that is a focal point of controversy in the context of universal screening in childhood. Lifestyle modifications in the form of dietary changes and increased physical activity remain the initial focus. NHLBI recommends that pharmacotherapy intervention be considered in children ≥10 years of age if LDL-C targets are not met with lifestyle changes, with a primary goal of reducing the LDL-C concentration to <130 mg/dL (<3.37 mmol/L) (1). Once LDL-C goals have been met, focus remains on the goal of reducing non–HDL-C to <145 mg/dL (<3.76 mmol/L). Statins and bile acid–sequestering agents may ultimately be considered; the safety and efficacy of both are supported by short-term studies; and both are approved for use in children. The long-term risks and benefits are not well delineated, however, and there are no data on the safety of initiating lifelong lipid-lowering therapy in childhood. Furthermore, it is unknown whether statin monotherapy in childhood will lead to an improvement in cardiovascular outcomes decades later. Given the paucity of long-term evidence-based outcome studies, parents are not likely to be overzealous about having their child treated with a statin, although some parents may be amenable to treatment in postpubescent adolescents.
Where Do We Go from Here?

Although a step in the right direction, are the NHLBI guidelines still too conservative? Lipid testing in children beginning at the age of 2 years remains the recommendation if there is a positive family history of CVD or dyslipidemia. There are arguably advantages to beginning universal screening at the age of 2 years, a time of early development when parents are generally engaged and vigilant about well-child checkups and when there are additional opportunities for provider–parent education about the importance of diet, exercise, and a healthy lifestyle. Furthermore, it would be possible to identify children and families with FH. A metaanalysis recently demonstrated that the use of total cholesterol alone may best discriminate between people with and without FH between the ages of 1 to 9 years (5), a time when there is less overlap in total cholesterol and LDL-C between affected and unaffected individuals. FH should be suspected in children with an LDL-C value >160 mg/dL (>4.14 mmol/L) or a non–HDL-C concentration >190 mg/dL (>4.92 mmol/L). Statin therapy is not recommended or indicated until the age of 10 years in most heterozygous FH patients, and modulation of risk factors becomes the primary goal. Point-of-care lipid testing or blood spot screening may be prudent for various screening strategies, although little evidence currently supports this concept. Attractive to the pediatric clinical community is the notion that screening may be conducted in children who are not fasting, and targeting non–HDL-C concentrations remains an acceptable practice. Although non–HDL-C is only a surrogate and not a direct reflection of the number of atherogenic apolipoprotein B–containing particles, in pediatrics it may work well enough for screening purposes.

Clearly the strategies and previous recommendations for assessing lipids and lipoproteins in children and adolescents were ineffective and missed detecting individuals in childhood who may now be manifesting relevant clinical signs and symptoms of CVD. A change to universal lipid screening for all children by the age of 9–11 years is a major improvement and one that I believe will lead to an improvement in cardiovascular outcomes later in life. Identification and early treatment of children with hyperlipidemia and dyslipidemia is critical; however, there is no avenue for treating an individual without initial possession of knowledge that treatment is required.

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