CME

Updated guidelines for lipid screening in children and adolescents

Taylor Howard, PA-C; John Grosel, MD

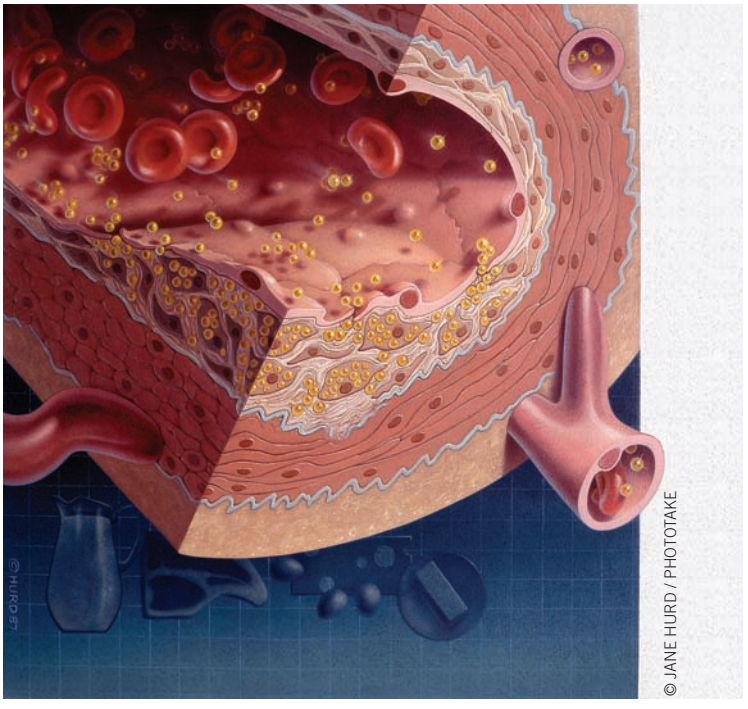
ABSTRACT

Elevated serum lipoproteins in childhood and adolescence are associated with health consequences and poor outcomes in adulthood. Universal screening, recommended in recent guidelines from the National Heart, Blood, and Lung Institute and supported by the American Academy of Pediatrics, may help identify a significant number of children who would be missed by targeted screening.

Keywords: lipid screening, obesity, pediatrics, adolescents, dyslipidemia, familial

Learning objectives

- Describe the current lipid screening guidelines for children and adolescents.
- Discuss controversy and concerns surrounding lipid screening guidelines in children and adolescents.
- Recommend treatment strategies for children and adolescents with elevated lipids.



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In response to the current childhood obesity epidemic, the National Heart Blood and Lung Institute (NHBLI) and American Academy of Pediatrics (AAP) now recommend universal serum lipid screening for children once between ages 9 and 11 years and again when they reach ages 17 to 21 years.[1] Targeted screening is recommended for children ages 2 to 8 years and 12 to 16 years who have cardiovascular risk factors such as hypertension, obesity, or a family history of premature cardiovascular disease. See **Table 1** for a summary of the updated screening guidelines.

The children and adolescents in the universal screening age groups are to receive a nonfasting lipid panel, which will calculate the non–high-density lipoprotein (non-HDL) cholesterol level by subtracting HDL cholesterol from the total cholesterol level. Non-HDL cholesterol has been identified as being more predictive of persistent dyslipidemia in children and adolescents than other lipoprotein levels.[1] Obtaining non-HDL cholesterol levels is practical and convenient because it can be accurately calculated in a nonfasting state. A fasting lipid panel, to determine individual serum lipoprotein levels, is only required if elevated levels of non-HDL cholesterol are detected from the nonfasting screening test. The convenient nonfasting test can be performed at annual well-child checks, without requiring any preparation.

The guidelines also provide easy-to-follow algorithms to assist clinicians with the screening process, risk factor management, and treatment of dyslipidemias (**Figure 1** and **Table 2**). Lifestyle modification, including specific meal plans and regular exercise, is the recommended initial treatment of dyslipidemias in children. However, if lifestyle modification is not sufficient to control the serum lipoprotein levels, pharmacologic intervention may be started.

Taylor Howard is a 2014 graduate of the Marietta College PA program in Marietta, Ohio. She practices at Dermatology Centers, Inc., in southern West Virginia. **John Grosel** is an associate professor in the Marietta College PA program and practices radiology at Riverside Radiology and Interventional Associates, Inc. The authors have disclosed no potential conflicts of interest, financial or otherwise.

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Key points

- Universal serum lipid screening is recommended for children ages 9 to 11 years and ages 17 to 21 years.
- Targeted screening is recommended for children ages 2 to 8 years and 12 to 16 years who have cardiovascular risk factors such as hypertension, obesity, or a family history of premature cardiovascular disease.
- Elevated serum lipoproteins in childhood and adolescence are associated with health consequences and poor outcomes in adulthood.
- Most children with dyslipidemia can be treated with diet and lifestyle modifications, although some will need pharmacologic therapy.

CONCERNS SURROUNDING THE UPDATED GUIDELINES

Previously, the NHBLI recommended targeted screening of all children and adolescents, regardless of age.[2] The expert panel that worked on the new guidelines claims that solely relying on targeted screening fails to identify many children with dyslipidemias. However, clinicians and the public have raised concerns about the validity, reliability, and predicted outcomes of the universal screening recommendations. Many opponents of the updated guidelines claim that universal screening is overaggressive, and also criticize the panel for failing to evaluate the potential harms and the cost-effectiveness of the new guidelines.[3,4] Some claim that a blood test is not needed to determine which children are overweight, obese, or need to improve their lifestyle choices.[5] Most clinicians agree about the importance of identifying and treating children with severe elevations of serum lipids, such as children who suffer from genetic familial hypercholesterolemia. But many clinicians argue against the need to identify and treat children with moderate dyslipidemias because these children will be treated with the lifestyle modifications already recommended for the entire population.[6] Furthermore, many children are anxious about needlesticks and may suffer psychologic effects from being labeled with dyslipidemia.[4,6]

Although the AAP supports the NHBLI's updated recommendations, the US Preventive Services Task Force (USPSTF) declared in 2007 that evidence is insufficient to recommend for or against routine screening of lipids in children and adolescents up to age 20 years.[7] The discrepancy between the two contrasting recommendations served as a major argument point of opponents.[6] However, in light of the present debate, the USPSTF is performing a detailed systematic review to update its recommendations.[7] These concerns have led to the recommendations not being fully accepted and implemented in practice, and have left many clinicians in a diagnostic dilemma.

TABLE 1. Summary of the updated lipid screening guidelines[1]

A fasting lipid is defined as two fasting lipid panels performed after 2 weeks but within 3 months of each other; average the results.

Patient age (years)	Recommendation
2-8	No routine lipid screening. Measure fasting lipid if: • Parent, grandparent, aunt, uncle, or sibling with myocardial infarction, angina, stroke, coronary artery bypass graft (CABG)/stent/angioplasty at <55 years (males) or <65 years (females). • Parent with total cholesterol ≥240 mg/dL or known dyslipidemia • Child has diabetes, hypertension, BMI ≥95th percentile or smokes cigarettes. • Child has a moderate- or high-risk medical condition that puts child at an accelerated risk.
9-11	Universal screening. Perform a nonfasting lipid panel or fasting lipid panel. Nonfasting lipid panel: Calculate non-HDL by subtracting HDL from total cholesterol. If non-HDL is 145 mg/dL or greater and HDL is less than 40 mg/dL, perform a fasting lipid panel. Fasting lipid panel: Repeat this test if LDL is 130 mg/dL or greater, non-HDL is 145 mg/dL or greater, HDL is less than 40 mg/dL, or triglycerides are 100 mg/dL or greater in a patient under age 10 years or 130 mg/dL in a patient 10 years and older.
12-16	No routine screening. Measure fasting lipid panel if the clinician has new knowledge of above-mentioned patient risk factors (however, for this age group, the BMI risk factor is defined as the 85th percentile or greater).
17-21	Universal screening. Perform a nonfasting lipid panel and calculate non-HDL cholesterol. • For patients ages 17-19 years, if non-HDL is 145 mg/dL or greater or HDL is less than 40 mg/dL, perform a fasting lipid panel. • For patients ages 20-21 years, if non-HDL is 190 mg/dL or greater or HDL is less than 40 mg/dL, perform a fasting lipid panel.

UNIVERSAL LIPID SCREENING

Universal screening hopes to categorize children into three possible classifications of dyslipidemias:

- children with undiagnosed familial hypercholesterolemia
- children with undiagnosed dyslipidemia due to secondary causes, such as diabetes or thyroid disease
- children with undiagnosed multifactorial dyslipidemia due to various risk factors and lifestyle.

Although dyslipidemias can have many causes, the most common cause in children and adolescents is obesity. These patients commonly have a moderate-to-severe elevation of triglycerides, a normal-to-mild elevation of low-density lipoprotein (LDL) cholesterol, and decreased HDL cholesterol levels. Knowing that a child's lipid levels are unsatisfactory may serve as an incentive or wake-up call for the patient and parents to assess and implement changes to ultimately reduce the child's risk for cardiovascular disease. See **Table 3** for acceptable, borderline, and elevated levels of serum lipoproteins in children and adolescents.

If the universal screening recommendation is to be embraced and implemented by primary care clinicians, the future health repercussions caused by elevated LDL cholesterol and total cholesterol levels in childhood and adolescence must be recognized by the public as well as the

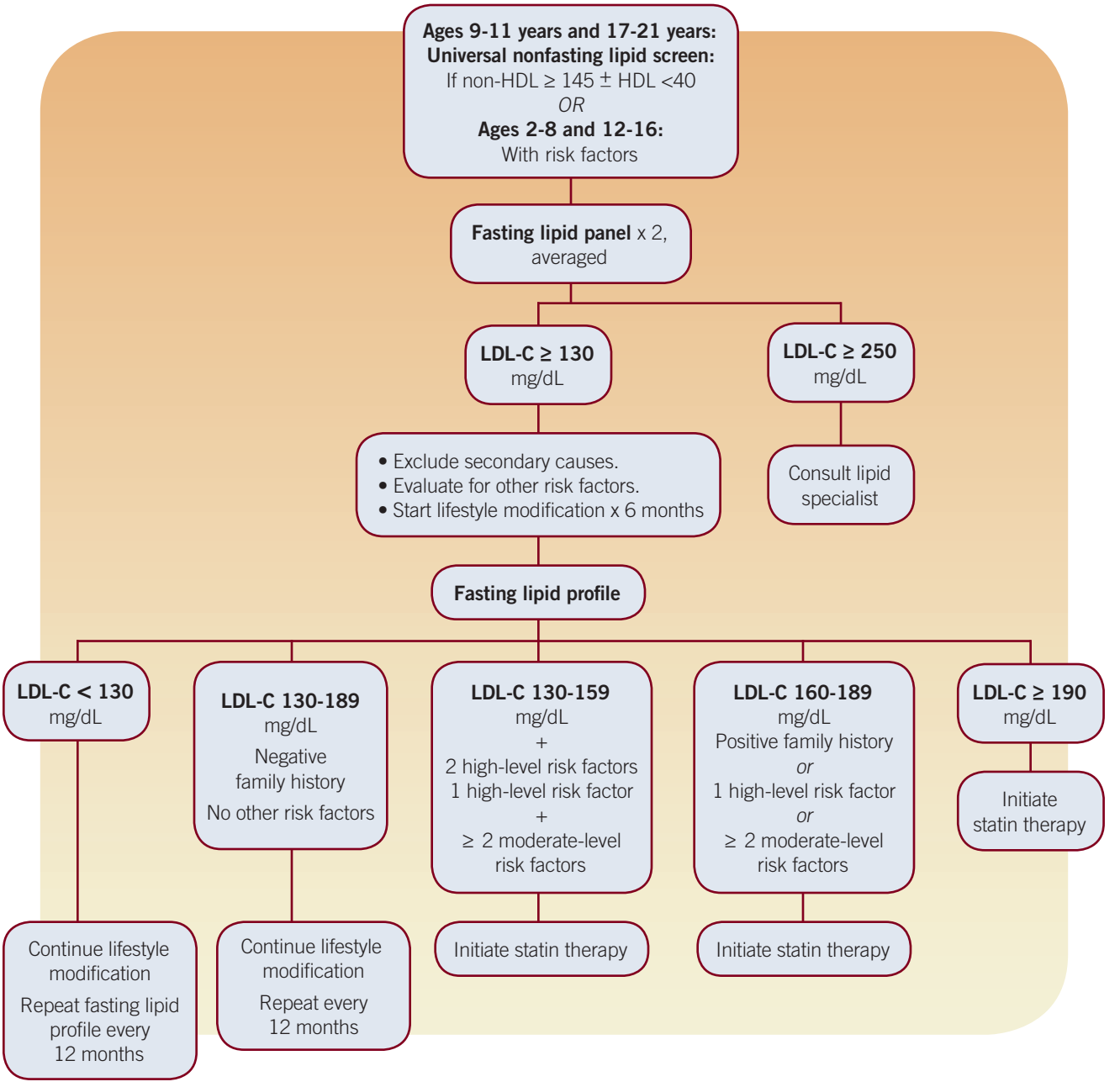

FIGURE 1. Summary of NHBLI's guidelines for the management of elevated serum LDL in children and adolescents[1]

medical community. Heart disease is the number one cause of death in the United States, and claims the lives of 600,000 patients annually.[8] But because patients with elevated lipoprotein levels typically are asymptomatic until clinical cardiovascular disease occurs, screening serum lipid levels is imperative for diagnosis, especially in young patients. With early detection of dyslipidemia through universal screening, clinicians can intervene promptly to delay patients' progression toward clinical disease.

TABLE 2: High- and moderate-level risk factors considered when determining management of elevated LDL cholesterol in children and adolescents[1]

High-level risk factors

- Hypertension that requires pharmacologic therapy (BP ≥99th percentile + 5 mm Hg)
- Cigarette smoker
- BMI ≥97th percentile
- Presence of high-risk conditions, such as type 1 or type 2 diabetes, chronic kidney disease, end-stage renal disease, postrenal or cardiac transplant, or Kawasaki disease with current aneurysm

Moderate-level risk factors

- Hypertension that does not require drug therapy
- BMI ≥95th but <97th percentile
- HDL cholesterol level less than 40 mg/dL
- Presence of moderate-risk conditions, such as Kawasaki disease with regressed coronary aneurysm, chronic inflammatory disease (systemic lupus erythematosus or juvenile rheumatoid arthritis), HIV infection, or nephrotic syndrome

ATHEROSCLEROTIC DISEASE STARTS EARLY

For universal lipid screening in children to be considered justifiable, scientific evidence must show that atherosclerotic disease begins in childhood and adolescence. Although the clinical manifestations of atherosclerotic disease are not typically obvious until later decades of life, precursor lesions are known to begin forming during adolescence. Well-known cadaver studies carried out on American soldiers during the Korean War were among the first to show the presence of precursor atherosclerotic lesions, known as fatty streaks.[9]

The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study determined that fatty streaks were a direct precursor lesion to adult fibrous plaques. Cadaver dissections showed that the pattern of distribution of fatty streaks in younger patients follows the distribution of raised atherosclerotic plaques in older patients, supporting the well-accepted theory today that atherosclerotic disease begins during childhood and adolescence.[10]

Elevated LDL cholesterol has been involved in the pathogenesis of atherosclerotic plaque and the cardiovascular disease that follows. However, the mere presence of elevated lipoproteins in adolescents does not warrant the need for screening. For lipid screening in children and adolescents to be warranted, evidence must support the theory that increased serum lipid levels and the presence of other cardiovascular risk factors in childhood and/or adolescence is directly related to decreased optimal cardiovascular health in adulthood. Such evidence exists: Several studies support the correlation between increased levels of LDL cholesterol in childhood and negative cardiovascular health during adulthood. Many of these studies also support the early diagnosis of dyslipidemias in children, claiming that it is essential in preventing the formation of atherosclerotic plaques and long-term sequelae that follow occlusive arterial disease.

The Young Finns Study, a prospective cohort study, examined the association between cardiovascular risk variables present in childhood or adolescence (elevated LDL-C levels, low HDL-C levels, elevated triglycerides, elevated systolic BP, BMI, and smoking) and increased common carotid artery intimal media thickness in adulthood. Carotid intimal media thickness is an important indicator for clinical coronary artery disease in adults. Increases in carotid intimal thickness are directly associated with an increased risk of future myocardial infarction and cerebrovascular accident in asymptomatic adults.[11] The study found that increased carotid intimal media thickness in adulthood was significantly associated with elevated childhood serum LDL levels, along with elevated systolic BP, elevated BMI, and smoking. LDL cholesterol levels above the 80th percentile for patients ages 12 to 18 years were directly related to increased carotid intimal media thickness measured in young adults. In addition, the authors found a correlation between the number of risk factors present in childhood and adult carotid intimal media thickness, concluding that exposure to multiple cardiovascular risk factors during childhood and adolescence may initiate endothelial damage and contribute to the development of atherosclerosis.[12]

The Bogalusa Heart Study, another commonly cited cohort study, also examined the association between traditional cardiovascular risk factors and carotid intimal media thickness in young adults. The study found that elevated BMI and elevated levels of LDL cholesterol during childhood significantly predicted increased carotid intimal media thickness in adulthood, with childhood LDL cholesterol levels showing the highest correlation.[13]

IDEAL CARDIOVASCULAR HEALTH STARTS YOUNG

The updated guidelines focus on lifestyle modifications and risk factor reduction. To justify universal screening, evidence must show that early intervention and risk reduction is safe and reduces overall cardiovascular mortality. A follow-up study of the Young Finns Study has shown an association

between ideal cardiovascular health during childhood and optimal cardiometabolic outcomes in adulthood. The authors concluded that ideal childhood cardiovascular health was inversely associated with carotid intimal media thickness levels.[14] However, this study was limited by the fact that measurement of diet and physical activity were not standardized. These findings support other claims that low levels of cardiometabolic risk markers in childhood are associated with thinner carotid intimal media thickness and lower risk of future atherosclerotic disease.[15,16] Other studies also support the importance of early diagnosis of dyslipidemia and early control of modifiable risk factors in preventing the long-term effects of arterial disease.[17] Previous research has shown that cardiovascular risk factors not only persist over time, but usually worsen with age.[17] Reducing cardiovascular risk factors in childhood through diet and lifestyle modifications has proven effective in correcting unfavorable serum lipid levels and preventing the formation of atherosclerotic disease.[1] This reduces the risk of future clinical cardiovascular disease, especially in children who suffer from multifactorial dyslipidemia.

TABLE 3. Low, acceptable, borderline, and high serum levels for common lipoproteins in children and adolescents[1]

	Low (mg/dL)	Acceptable (mg/dL)	Borderline (mg/dL)	High (mg/dL)
Total cholesterol	n/a	<170	170-199	≥200
LDL	n/a	<110	110-129	≥130
Non-HDL	n/a	<120	120-144	≥145
Triglycerides in patients ages 0-9 years	n/a	<75	75-99	≥100
Triglycerides in patients ages 10-19 years	n/a	<90	90-129	≥130
HDL	<40	>45	40-45	n/a

PHARMACOLOGIC INTERVENTION

Reducing modifiable cardiovascular risk factors in children and adolescents with genetic dyslipidemia often fails to improve serum lipid levels. In children and adolescents with genetic dyslipidemia and in those with multifactorial dyslipidemia who fail to adopt or respond to lifestyle modification, statins have been shown to be effective at lowering serum LDL cholesterol levels and preventing the progression of atherosclerotic disease, with no adverse effects on growth, development, or sexual maturation.[1] Pharmacologic treatment in children with a severe elevation of LDL cholesterol is based on the assessment of lipid levels and the presence of associated cardiovascular risk factors.[1] Controversy exists and many opponents of the new recommendations express concern that most children identified with elevated lipoproteins will be placed on lipid-lowering medication.[4,18,19] However, pharmacologic treatment typically is needed for children who are nonadherent with lifestyle modification, or who have genetic familial hypercholesterolemia unresponsive to lifestyle modification. One study found that only 0.8% of adolescents ages 12 to 17 years were potentially eligible for pharmacologic treatment based on elevated serum LDL cholesterol levels.[20]

Although long-term studies on the use of statins in children are lacking, short-term studies have shown very promising results. Multiple statins have been approved by the FDA for use in children as young as age 10 years, including atorvastatin, fluvastatin, lovastatin, rosuvastatin, and simvastatin; pravastatin has been approved for use in children as young as age 8 years.[21-26] A Cochrane review that analyzed eight randomized placebo-controlled trials found that statins were responsible for a significant reduction in both serum total cholesterol and serum LDL cholesterol concentrations in children with familial hypercholesterolemia. Regarding statins' safety and adverse reactions, the review found no significant increase in liver transaminase levels, creatine kinase values, or differences in respect to sexual maturation in treatment groups versus those who received placebo.[27]

One study of children ages 8 to 18 years with familial hypercholesterolemia demonstrated that initiation of statin therapy at a young age was associated with a subsequently thinner carotid intimal media thickness after follow-up when compared with initiation at an older age.[28] This suggests that patients with familial hypercholesterolemia may benefit from earlier initiation of pharmacologic therapy.[28] Other studies also support earlier treatment in children with genetic dyslipidemia. A recent study found that children affected with familial hypercholesterolemia have greater mean baseline carotid intimal media thickness compared with their unaffected siblings; this difference is significant as early as age 8 years.[29]

Although research supports the efficacy and safety of statins in children and adolescents, pharmacologic treatment should not be started without first instructing and encouraging the specified lifestyle and diet modifications provided by the expert panel.

IS UNIVERSAL SCREENING NECESSARY?

For universal screening to be rational, it must provide a more reliable means of recognizing and identifying children and adolescents with dyslipidemia than the previously recommended targeted screening. But do the new guidelines identify significantly more children with dyslipidemia—children who would have been missed previously? According

to the expert panel, using a positive family history of dyslipidemia or premature cardiovascular disease as the main factors in determining the need for screening misses 30% to 60% of children with dyslipidemia.[1] Other studies support these views. The CARDIAC Project found that a positive family history is not a singularly reliable indicator for lipid screening. Of 20,266 fifth-grade students included in the study, 28.6% did not meet the guidelines for testing based on a negative family history. Of the students with no family history, 9.5% had dyslipidemia, and 1.7% of those children had LDL cholesterol levels of 160 mg/dL or greater, warranting pharmacologic intervention. The authors support universal screening, stating that family history as an indication to determine the need for cholesterol screening misses many children with moderate dyslipidemias, and fails to detect a substantial number of children with genetic familial hypercholesterolemia that would likely require pharmacologic treatment.[30]

Project Heart Beat, a longitudinal study, examined the sensitivity, specificity, and positive predictive value of lipid screening in children using:

- a positive family history alone
- BMI in the 85th or greater percentile alone
- a positive family history plus a BMI in the 85th or greater percentile.

The authors concluded that using any of the three screening criteria may still miss a significant number of children with dyslipidemia.[31] These data support the application of universal screening in children and adolescents, which will help identify children with dyslipidemia who may have been missed by targeted screening.

WHAT WILL IT COST?

The expert panel did not attempt to estimate the cost-effectiveness of universal lipid screening.[3,4] Current studies are lacking, and research needs to be undertaken to determine if universal screening reduces future spending on cardiovascular health. From a health standpoint, the benefit of screening outweighs the risk; earlier identification and pharmacologic treatment of children with dyslipidemia will prevent or postpone clinical cardiovascular disease, most likely reducing overall healthcare spending. However, until long-term follow-up studies have been conducted, the improvement in cardiac endpoint results and total cost savings are unknown.

CONCLUSION

Universal serum lipid screening in children ages 9 to 11 years and adolescents ages 17 to 21 years is now the NHBLI's recommendation, with targeted screening for all other age groups. Relying exclusively on targeted screening fails to identify a significant number of children with dyslipidemia. A nonfasting lipid profile to calculate the non-HDL cholesterol level is recommended for the initial screening. Most children and adolescents with unfavorable serum lipid levels can be treated with lifestyle and diet modifications; a small percentage will need pharmacologic treatment. Normalizing serum lipid concentrations early in life reduces the incidence and severity of atherosclerotic disease later in life. Considering the epidemics of childhood obesity and diabetes, clinicians should use these screening guidelines and be aware of the implications of dyslipidemia in young patients. **JAAPA**

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