HHS Public Access

Author manuscript

JAMA. Author manuscript; available in PMC 2015 March 04.

Published in final edited form as:

JAMA. 2012 January 18; 307(3): 259–260. doi:10.1001/jama.2011.2012.

Is Universal Pediatric Lipid Screening Justified?

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In Late 2011, an Expert Panel Convened by the National Heart, Lung, and Blood Institute (NHLBI), of which we were members, released a set of integrated guidelines for cardiovascular health in youth comprising numerous clinically useful recommendations.[1] However, one new recommendation, about which the 2 of us disagree, merits further scrutiny: to perform lipid screening on all children at 9 to 11 years of age, followed by a comprehensive scheme for further evaluation and treatment. Just 4 years previously, the US Preventive Services Task Force (USPSTF) concluded that evidence is insufficient to recommend for or against screening for lipid disorders in childhood.[2] Both of the guideline committees used an explicit evidence-based approach to answer key questions, with extensive literature searches, critical review of relevant studies, and analogous grading schemes. How could the 2 guidelines be so different? The evidence base has advanced in 4 years, but not enough to explain such a discrepancy. What is a clinician who cares for children to do in the face of this ambiguity?

Evaluating any screening program involves weighing benefits against harms and costs. The ideal evaluation features a large randomized controlled trial of screening. Given the decades between initial testing and adult health outcomes, however, no such trial will ever exist for cardiovascular risk factor screening in childhood. In the absence of such a trial, evidence must be combined from shorter-term studies of measurement variability, tracking, prediction, intervention effectiveness, cost, and harm.

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Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Gillman reported giving invited talks in meetings sponsored by the International Life Sciences Institute, Nestle Nutrition Institute, and Danone; receiving royalties from UpToDate for a chapter on dietary fat; and providing external reviews for the US Preventive Services Task Force. Dr Daniels reported being on a data and safety monitoring board for Merck Schering Plough and QLT and receiving royalties for a book chapter from McGraw-Hill. Between 1985 and 2003, Dr Gillman was a primary care internal medicine/pediatrics physician at South Boston Community Health Center. Since 2005, he practices in the Preventive Cardiology Clinic at Children's Hospital Boston. Dr Daniels is a pediatric cardiologist focused on preventive cardiology. Hehas directed clinical programs in obesity, hypertension, and dyslipidemia and currently practices in the Preventive Cardiology Clinic at Children's Hospital Colorado.

Additional Information: Dr Daniels was the chair and Dr Gillman was a member of the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents convened by the National Heart, Lung, and Blood Institute.

Additional Contributions: Lee Goldman, MD, MPH (Columbia University College of Physicians and Surgeons), and Emily Oken, MD, MPH (Harvard Medical School), provided comments on a previous draft of the manuscript. Neither received compensation from a funding sponsor for their contributions.

As reviewed by the NHLBI Expert Panel, an increasing number of these shorter-term studies provide support for the potential benefits of routine pediatric lipid screening to detect and treat children with elevated levels of low-density lipoprotein cholesterol (LDL-C). First, the atherosclerotic process begins in childhood, and pathology studies demonstrate that higher levels of LDL-C are associated with the presence and severity of atherosclerotic lesions. Second, cholesterol levels track from childhood to adulthood, and cumulative exposure to dyslipidemia appears to be associated with cardiovascular risk later in life. Third, reducing LDL-C levels in childhood appears to delay atherosclerosis at least among patients with the heterozygous form of familial hypercholesterolemia, which occurs in approximately 1 in 500 individuals and is associated with relatively high rates of cardiovascular disease in middle age, including sudden cardiovascular death. Fourth, relying on family history to drive the screening process, advocated by the American Academy of Pediatrics in 2008 and a previous NHLBI-sponsored panel in 1992, will miss many children with elevated LDL-C levels.[3, 4]

However, even together these factors do not necessarily amount to a solid rationale for universal screening. Most randomized trials of lipid lowering in youth are relatively short and involve medication treatment of high-risk children. The extent to which lifestyle intervention reduces long-term risk in those with moderately elevated lipid levels is unknown. Also unclear are the presence of psychological effects from labeling and safety for children taking statins for long periods. In addition, although the initial screening test can be nonfasting, additional blood draws in the fasting state are needed to confirm diagnosis, and the acceptability of these procedures to children and parents is an open question. Dietary changes to lower LDL-C are difficult to maintain, and long-term adherence to medication in asymptomatic individuals is low.

Furthermore, moderately strong tracking of a risk factor over time does not translate into high sensitivity and specificity for the risk factor to predict later disease,[5] and because the incidence of ischemic heart disease in young to middle-aged adults remains low, even a high sensitivity and specificity would still yield a low positive predictive value across the entire population. In other words, most children identified as having moderate dyslipidemia will not develop premature heart disease. The number of these “false positives,” who accrue cost and risk but do not benefit from screening, will increase by expanding family history–directed screening to universal screening. Also, although the cost of a single lipid measure may appear trivial, major costs will ensue from aggregating over the population, thorough workups and long-term intervention. Even in randomized trials, behavioral interventions to achieve modest reductions in LDL-C require substantial resources.

The choice of key questions in the guideline development process can explain why committees sometimes do not fully consider such competing issues, and in particular, why the NHLBI Expert Panel and the USPSTF came to different conclusions (Table). The key questions of the USPSTF[2] were more balanced, although this committee overlooked surrogate markers of atherosclerosis to assess intervention benefits. Surrogate markers maybe credible alternatives to clinical end points to assess cardiovascular risk in youth. In contrast, the NHLBI Expert Panel[1] key questions did not explicitly include essential issues

regarding accuracy and adverse effects, thus potentially underestimating risk and tipping the balance in favor of screening.

To arrive at reasonable policies about pediatric lipid screening, guideline panels not only need to ask the right questions but also must have away to integrate the answers. One method is decision analytic modeling. A recent study of long-term effectiveness and cost-effectiveness of childhood blood pressure screening, for example, showed that compared with the population-wide policy approaches of reducing the salt content of food and promoting physical education, blood pressure screening—whether universal or selective—both costs more and is less effective.[6]

In the same year, when one group of authors suggests that age exceeding 55 years should be the only screen for cardiovascular risk,[7] and another group recommends universal lipid screening at age 10 years accompanied by a detailed algorithm for follow-up and treatment,[1] it is apparent that whether, whom, and how to screen are still open questions. While awaiting the results of research to clarify these issues, the 2 of us agree on the current state of the evidence and the areas of uncertainty. We also agree that along with adoption of population approaches to cardiovascular disease prevention early in life, there is value in detection and treatment of the highest-risk children (those who have severe elevation of LDL-C as a result of familial hypercholesterolemia). Where we differ is in the detection approach and whether it is worthwhile to identify and treat children with moderately elevated levels of LDL-C.

One of us (S.R.D.) puts a premium on the identification and intensive treatment of as many individuals as possible with familial hypercholesterolemia, which requires a universal screening approach. Individuals with moderate dyslipidemia, also identified by universal screening, may benefit from lifestyle interventions that are already recommended for the entire population by numerous guidelines with no evidence of harm. Such lifestyle interventions are designed to lower the lifetime risk of cardiovascular disease, which is the leading cause of death in the United States. A low-risk profile, which includes a low cholesterol level, measured in adulthood is associated with very low probability of developing cardiovascular disease and a long disease-free lifespan.[8] This author believes that universal screening and improvement of lifestyle in childhood is necessary to achieve adult low-risk status for the largest number of individuals.

The other author (M.W.G.) puts a premium on the principle that screening requires a very high burden of proof. Because physicians initiate screening for asymptomatic individuals and the harms of screening fall disproportionately on the healthy, primum non nocere is paramount. Universal pediatric lipid screening is not justified because it will identify a large number of children who can only experience harm along with a limited number of children for whom there is potential (but uncertain) benefit, and it incurs large costs. Until better information is available on the balance of these competing factors, this author believes that it is reasonable for clinicians providing care for children in the United States to screen more narrowly based on family history and then reserve treatment for adolescents with LDL-C levels high enough to signify familial hypercholesterolemia.[9]

Acknowledgments

Funding/Support: This research was supported in part by grant K24 HL 068041 to Dr Gillman.

Role of the Sponsors: The funding source had no role in the preparation, review, or approval of this article.

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Table

Key Questions in 2 Guidelines Addressing Pediatric Lipid Screening

	No. of Key Questions in Each Category	
Categories	**USPSTF[2]**	**NHLBI Expert Panel[1]**
Overall effectiveness	1	0
Natural history, pathophysiology	2	11
Accuracy of screening tests	4	0
Adverse effects of screening	1	0
Treatment effectiveness		
Short term	4	4
Long term	2	2
Adverse effects of treatment	1	0
Cost, cost-effectiveness	0	0