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Overly Aggressive New Guidelines for Lipid Screening in Children: Evidence of a Broken Process

AUTHORS: Thomas B. Newman, MD, MPH,^{a,b} Mark J. Pletcher, MD, MPH,^{a,c} and Stephen B. Hulley, MD, MPH^a

Departments of ^aEpidemiology and Biostatistics, ^bPediatrics, and ^cMedicine, School of Medicine, University of California, San Francisco, California

KEY WORDS

cholesterol, screening, health policy, conflict of interest, lipoprotein

ABBREVIATIONS

CVD—cardiovascular disease

NHLBI—National Heart Lung and Blood Institute

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Address correspondence to Thomas B. Newman, MD, MPH, Department of Epidemiology and Biostatistics, UCSF Box 0560, San Francisco, CA 94143. E-mail: newman@epi.ucsf.edu

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A new expert panel report¹ released by the National Heart Lung and Blood Institute (NHLBI) and endorsed by the American Academy of Pediatrics² recommends universal screening of 9- to 11-year-old children with a nonfasting lipid panel and targeted screening of 2- to 8-year-old and 12- to 16-year-old children with 2 fasting lipid profiles. These guidelines were developed in parallel with adult guidelines due out later this year, using what are described as “state-of-the-art principles of evidence-based medicine.”³ The process is designed with the laudable intentions of improving transparency, keeping recommendations closely tied to the evidence, and indicating where evidence is strong and where guidelines are based on expert opinion. However, we believe that the high evidence grades for the extremely aggressive pediatric lipid recommendations are inaccurate and unjustified and that the conflicts of interest reported by panel members are too substantial to ignore. In short, these guidelines provide evidence that the NHLBI’s new “evidence-based” guideline process did not achieve its goals.

The guidelines we examine here are related to lipid screening, but similar concerns apply to screening children for hypertension discussed in the same NHLBI report.¹ Many of our concerns are discussed in Chapter 3 of this report, which was omitted from the supplement published in *Pediatrics*² and appears to have been ignored by the subcommittee that drafted the lipid screening recommendations. Two recent commentaries in JAMA complement our concerns as to the wisdom and appropriateness of these pediatric lipid screening guidelines.^{4,5}

The NHLBI screening recommendations are overly aggressive. The 2- to 8-year-old and 12- to 16-year-old children for whom the panel strongly recommends 2 fasting lipid panels are those who have diabetes, hypertension, or a BMI above the 95th percentile; who smoke cigarettes; who have a parent with a total cholesterol level of ≥ 240 mg/dL or known dyslipidemia; or who have a parent, grandparent, aunt, or uncle who has had a stroke or coronary artery disease before age 55 for men and 65 for women.² Approximately 30% to 40% of children will meet the family history criteria for screening,⁶ and many more will qualify for screening based on the other criteria. All of these children will need to go to the laboratory and have their blood drawn before breakfast on 2 occasions for fasting lipid panels (a logistical and emotional challenge for most families). If their low-density lipoprotein cholesterol is ≥ 130 mg/dL (as it is in $\sim 10\%$ of unselected girls⁷ (p. 534)), they are to be placed on a special “CHILD-1” diet, and fasting lipid panels are to be repeated every 6 to 12 months indefinitely, even if their lipid values became “acceptable” to the Expert Panel. Despite the fact that girls have higher lipid levels than boys but are at much lower age-specific cardiovascular

disease (CVD) risk in the ensuing decades, a single set of treatment cutoffs is used for both genders; given gender-specific lipid distributions⁷ (p. 534), implementation of this feature of the panel's guidelines would lead to more treatment of preschool girls than of teenage boys. Nonetheless, the panel rated these recommendations "Evidence Grade B," indicating "overwhelmingly consistent evidence from observational studies" (Table 1).

We agree with the panel that there is compelling evidence that cumulative exposure to risk factors such as high low-density lipoprotein cholesterol levels and hypertension in young or middle-aged adults increases the risk of atherosclerosis, that treatment of these risk factors in middle-aged and older adults reduces the risk of CVD events, that treatment of high cholesterol in children with familial hypercholesterolemia can reduce atherosclerotic disease indicators, and that people at higher risk of having these risk factors as adults can be identified by their childhood levels. The chain of evidence cited by the panel, however, contains weak links, notably the absence of even observational evidence or modeling to estimate the clinical event benefits of screening for and intervening on these risk factors in children. As they put it, "The evidence review supports the *concept* [emphasis added] that

early identification and treatment of dyslipidemia ... will substantially reduce clinical CVD risk." However, there is a vast difference between evidence to support a concept and the studies of clinical events, actual benefits and harms over the ensuing decades, that would be needed for these guidelines to qualify as evidence-based.

Importantly, there is also no quantification or even discussion of many of the harms that might result,⁸ such as dietary neuroses, family conflict, and CVD anxiety.^{9–12} There is also no estimate of how many children would be tested with fasting lipid panels, how many would be referred to a registered dietician or lipid specialist, how many extra follow-up visits would be needed, or how many children would ultimately "require" medication. The panel states that the acceptability to parents and children of obtaining fasting lipid levels "is an open question"¹ (p. 56). In fact, studies that have addressed acceptability of lipid testing in children find the majority of families do not comply.^{13–15}

Targeted screening with fasting lipid panels was "strongly recommended," meaning that the panel believes that "the benefits of the recommended approach clearly exceed the harms." The implication of this recommendation is that clinicians should follow it regardless of patient preferences unless "a clear and compelling rationale for an alternative approach is present." It is admittedly difficult to estimate average benefits and weigh those against harms, but such an attempt must be made to be confident that benefits "clearly exceed the harms." Furthermore, although the panel acknowledges that the "cost to society at large will likely be a major factor in decisions regarding screening"¹ (p. 59), rather than trying to estimate these costs before issuing their guidelines, the recommendations state only that "well considered cost-effectiveness analyses

of childhood [cardiovascular] risk factor screening should be a priority for future research"¹ (p. 60). Without these estimates, how can the panel be confident that the guidelines are reasonably cost-effective?

It is clear that the specific guidelines of which children to screen and treat are based on expert opinion and not firmly backed by clinical trials, observational studies, or even modeling. There is nothing inherently wrong with basing guidelines on expert opinion in disease situations for which therapeutic decisions must be made when relevant studies have not been done. The present policy, however, proposes an intervention applied to a healthy and asymptomatic population, with an enormous impact on costs and the potential to transform well children into patients with a chronic disease label ("dyslipidemia"). As dissenting panel member Matthew Gilman wrote, "Because physicians initiate screening for asymptomatic individuals and the harms of screening fall disproportionately on the healthy, *primum non nocere* is paramount."⁵ In fact, the panel report states, "a recommendation for universal screening requires a high burden of proof"¹ (p. 50), yet the panel seems to have ignored this sensible precept.

The greater a guideline's reliance on expert opinion, the more important it is to avoid even the appearance of conflict of interest. Yet the majority of panel members, including those responsible for drafting the lipid and lipoprotein chapter, disclosed an extensive assortment of financial relationships with companies making lipid-lowering drugs and lipid-testing instruments (Table 2). Accepting money from industry constitutes a conflict of interest that is not ameliorated by disclosure. That so many panel members with conflicts of interest were selected to draft the pediatric lipid guidelines undermines the credibility of

TABLE 1 Evidence Grading System Used for the Expert Panel's Report

Grade	Evidence
A	Well-designed randomized controlled trials (RCTs) or diagnostic studies performed on a population similar to the guidelines' target population
B	RCTs or diagnostic studies with minor limitations; genetic natural history studies; overwhelmingly consistent evidence from observational studies
C	Observational studies (case-control and cohort design)
D	Expert opinion, case reports, or reasoning from first principles (bench research or nonhuman animal studies)

TABLE 2 Financial Disclosures of the Expert Panel Chair and of the Members of the Subgroup Who Drafted the Lipids and Lipoproteins Chapter of the Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents¹

Panel Member	Reported Relevant Relationships
Stephen R. Daniels, MD, PhD, Panel Chair	Consultant or advisory board member: Abbott Laboratories, ^a Merck, ^b Schering-Plough ^c Funding/grant support for research: National Institutes of Health
Peter O. Kwiterovich, MD, Subgroup Leader	Consultant or advisory board member: Merck ^b , Schering-Plough, ^c Pfizer, ^d Sankyo, ^e LipoScience, ^f and Astra Zeneca ^g Speakers bureau: Merck, ^b Schering-Plough, ^c Pfizer, ^d Sankyo, ^e Kos, ^h and Astra Zeneca ^g Grant funding: Pfizer, ^d Merck, ^b GlaxoSmithKline, ⁱ Sankyo, ^e and Schering-Plough ^c
Patrick E. McBride, MD, MPH	Consultant or advisory board member: Bristol-Myers Squibb ^j and Merck ^b Speakers bureau: Kos, ^h Merck, ^b and Pfizer ^d (none since July 2007)
Brian W. McCrindle, MD, MPH	Consultant or advisory board member: Abbott Laboratories, ^a Bristol-Myers Squibb, ^j Daichii-Sankyo, ^k and Roche ^l Grant Funding: Astra Zeneca, ^g Sankyo, ^e Merck, ^b Schering-Plough, ^c and the National Institutes of Health

^a Abbott Laboratories produces the following relevant medications: ADVICOR (niacin extended-release/lovastatin), CONTROLIP (fenofibrate; not sold in the United States), NIAPAN (niacin extended release), SIMCOR (simvastatin/niacin extended-release), TriCor (fenofibrate), and TRILIPIX (fenofibric acid). Abbott Laboratories produces the following relevant diagnostic instruments: ARCHITECT ci16200 Integrated System, ARCHITECT ci4100 Integrated System, ARCHITECT ci8200 Integrated System, ARCHITECT i1000SR, ARCHITECT i2000SR, ARCHITECT i4000SR, and AxSYM.

^b Merck produces the following relevant medications: MEVACOR (lovastatin), VYTORIN (ezetimibe/simvastatin), ZETIA (ezetimibe), and ZOCOR (simvastatin).

^c Schering-Plough: see Merck.

^d Pfizer produces the following relevant medications: CADUET (amlodipine besylate/atorvastatin calcium), COLESTID (micronized colestipol hydrochloride), LIPITOR (atorvastatin calcium), and LOPID (gemfibrozil, USP).

^e Sankyo produces the following relevant medication: WELCHOL (colesevelam hydrochloride).

^f LipoScience produces the following relevant product: NMR LipoProfile.

^g Astra Zeneca produces the following relevant medication: CRESTOR (rosuvastatin calcium).

^h Kos: see Abbott Laboratories.

ⁱ GlaxoSmithKline produces the following relevant medication: LOVAZA (omega-3-acid ethyl esters).

^j Bristol-Myers Squibb produces the following relevant medication: PRAVACHOL (pravastatin sodium).

^k Daichii-Sankyo: see Sankyo.

^l Roche produces the following relevant products: ACCUTREND PLUS System, COBAS c 111 analyzer, COBAS INTEGRA Systems, COBAS 4000 analyzer series, COBAS 6000 analyzer series, COBAS 8000 modular analyzer series, MODULAR ANAlyTICS EVO solution, and REFLOTRON Systems.

both the guidelines and the process through which they were produced.

The guidelines also demonstrate the need to examine the system for grading evidence, particularly for population screening. Although the definition of “A” level evidence clearly specifies the need for randomized trials in relevant

populations, it should be revised to clarify that the trials must be of the intervention being recommended and that the endpoints must be clinically meaningful. Similarly, the “overwhelmingly consistent evidence from observational studies” must address the specific screening program being recommended,

and the outcomes of these studies must include clinical events. Observational studies that support a concept with evidence relating risk factors to surrogate outcomes (such as blood lipid levels) are not sufficient. The US Preventive Health Services Task Force recognized this in recommending that there was insufficient evidence to recommend childhood cholesterol screening.¹⁶

Finally, we need to move past the era when experts propose (and organizations endorse) guidelines with enormous societal costs without making any attempt at estimating cost-effectiveness. The NHLBI Panel is not alone in ignoring this; even the US Preventive Health Services Task Force's recommendations do not consider (financial) costs.¹⁷ As a result, any intervention with nonzero benefit may be recommended, regardless of how much it costs and how much better health might be achieved by investing those resources elsewhere. This is not sustainable.

We need evidence that will allow us to estimate health benefits, risks, and costs of proposed interventions and experts without conflicts of interest to help us synthesize this information. The expert panel's recommendations on lipid screening fall so far short of this ideal that we hope they will trigger a reexamination of the process through which they were produced.

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READING THE NOTE: *At the end of each clerkship rotation, I have to read and grade several clinical encounter notes that students write during their graded clinical skills examination. While that does not sound too onerous, it requires an enormous amount of time to read, correct, and assign a grade to more than 80 notes every few weeks. I have always wondered if this could be automated. Evidently, it can. As reported in The New York Times (Business: June 10, 2012), standardized tests administered by the states to high school students at the end of the school year often have an essay-writing component. Grading these typically requires humans to read each one. However, computer software programs have been developed that score the essays at least as well as humans do. In a study sponsored by the Hewlett Foundation, commercially available automated essay-scoring programs produced scores identical to those of human graders. This is a growing field as the implications are enormous. Most importantly for states, the cost of grading essays can be minimized. Many states, citing the costs involved, assess student writing prowess less often than desired. Also, the software can be modified to evaluate almost any writing exercise and can be set up so that lengthy explanations and practice exercises are included in the report to each student. A recent essay-scoring competition offered \$60,000 for first prize and drew 159 entries. The winning entry used typical computers used in classrooms and small data sets to generate remarkably accurate assessments. While the software is incredible, humans still need to review the essays, as students can potentially game the system by writing factual nonsense that computers cannot easily detect. As for me, I am dumbfounded by the finding that the average human reader of standardized school essays only spends three minutes on each essay. While I would like to think that I might be a better essay grader than a computer because I spend much more time than that on each note, I suspect that is probably not the case. I think I will investigate one of these programs so I can concentrate on clinical decision making rather than the mechanics of the note.*

Noted by WVR, MD

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