Screening for lipid disorders in children and adolescents can identify 2 types of lipid disorders: primary lipid disorders, which typically are monogenic, rare, and severe, and the more common secondary lipid disorders that often result from other disease processes or lifestyle behaviors (such as poor nutrition or inadequate activity) and are often less severe. The most common primary lipid disorder of childhood is familial hypercholesterolemia (FH), which is present in 1 in 250 to 350 children. Familial hypercholesterolemia causes markedly elevated levels of low-density lipoprotein cholesterol (LDL-C) starting at birth, and, if untreated, is associated with a 2- to 4-fold increase in morbidity and mortality from coronary heart disease in adulthood. Because of the relatively high prevalence and substantial long-term health risks of FH, the US Centers for Disease Control and Prevention previously designated it as a “tier 1” genetic condition, defined as having the potential for significant positive impact on public health if identified and treated. The opportunity to identify and treat FH earlier is the main motivation for childhood lipid screening.

Universal lipid testing in childhood will identify at least 1 abnormal lipid value in 1 of every 5 children aged 12 to 19 years. Unlike the severe elevations in LDL-C level observed in children with FH, these are predominantly mild abnormalities in levels of triglycerides and high-density lipoprotein cholesterol from secondary lipid disorders, often due to lifestyle behaviors. The International Childhood Cardiovascular Cohort (i3C) Consortium demonstrated that each per-unit increase in unhealthy levels of cholesterol and other risk factors during childhood was associated with a 2.7-times higher risk of fatal cardiovascular events in adulthood. However, the increased cardiovascular risk from the mild lipid abnormalities of secondary lipid disorders manifests in middle age or later, so the benefits of their early identification have been difficult to quantify.

In this issue of JAMA, the US Preventive Services Task Force (USPSTF) issues its latest recommendation on childhood lipid screening based on an updated review of evidence. As in 2007 and in 2016, the task force again finds evidence insufficient to recommend for, or against, screening for lipid disorders in childhood, including both genetic conditions such as FH and secondary multifactorial lipid disorders—an I statement. This USPSTF recommendation is anchored in uncertainty about long-term benefits and safety of screening for, identifying, and treating childhood lipid disorders and uncertainty about the optimal age to start lipid-lowering therapy (ie, in childhood vs. adulthood). At the crux of the controversy is the distinction between childhood screening for FH and general childhood lipid screening, as the latter will predominantly identify secondary lifestyle-related lipid abnormalities.

What are the implications of foregoing universal childhood lipid screening? The impact of delayed treatment of secondary lipid disorders is uncertain. Lifestyle-related secondary lipid disorders in children improve modestly with behavioral counseling on nutrition and physical activity. In the general population these interventions are likely safe in the short and long term and are associated with favorable subclinical vascular profiles, but there are no published studies examining the role of pharmacotherapy for secondary lipid disorders in children. In contrast, the impact of not screening children to identify primary lipid disorders like FH is clearer. In the absence of universal screening, current usual care fails to identify as many as 9 of 10 individuals meeting phenotypic criteria for FH. In many cases, FH is first diagnosed at the time of an early myocardial infarction, since the USPSTF recommends lipid testing in adults starting at age 40 years as a part of risk stratification, and many patients with FH will develop cardiovascular disease before this age. Treating FH during childhood slows the progression of vascular findings of atherosclerosis. One seminal study of 214 children showed that FH is associated with markedly lower rates of atherosclerotic cardiovascular disease events during 20 years of follow-up (1% among those treated in childhood compared with 26% in parents with FH not treated during childhood). A childhood diagnosis of FH also allows cascade screening of other family members who may be at increased risk of premature cardiovascular disease. Delayed identification of FH therefore has substantial implications for the child and their family.

In the absence of universal screening, clinicians rely on targeted lipid screening—typically based on a family history of premature atherosclerotic cardiovascular disease or comorbid conditions such as obesity. But this targeted approach would miss the majority of children with lipid disorders. For instance, in the West Virginia Coronary Artery Risk Detection in Appalachian Communities Project, LDL-C levels in the range for FH (≥160 mg/dL) were found in more children without a family history of premature atherosclerotic cardiovascular disease events or elevated cholesterol levels than in those with a high-risk family history (1.7% vs 1.2%). Family history-based screening also relies on parents knowing their full family history, which is often reported inaccurately or incompletely.
Opinion Editorial

From a health system perspective, the USPSTF’s determination of insufficient evidence may discourage the development or implementation of initiatives focused on identifying FH in youth using lipid testing, including electronic health record–based screening prompts. Clinicians may deprioritize ordering the screening tests, despite the fact that they routinely screen for conditions rarer than FH: newborn screening commonly includes testing for hypothyroidism (1 in 3000 to 4000) and phenylketonuria (1 in 23 930). Lipid and genetic screening for FH has been successfully performed alongside standard childhood immunizations. In the fragmented US health system, payers already have little incentive to treat conditions with long lead times, like FH, since the payer covering childhood screening and treatment is unlikely to reap the benefits of the averted cardiovascular event in middle age.

Moving beyond the USPSTF’s I statement will require new evidence. The USPSTF Evidence Review for key questions was restricted to randomized clinical trials with intermediate and long-term outcomes and cohort studies that assessed screening yield; expanding it to other study types, such as mendelian randomization studies, qualitative studies of patient and family impact and computer simulation modeling studies, would substantially expand the evidence base.

For instance, a meta-analysis of mendelian randomization studies showed the presence of beneficial variants in FH causative genes was associated with a 3-fold greater reduction in the risk of coronary heart disease per unit lower LDL-C level than that achieved with statin treatment started later in life, supporting LDL-C lowering during childhood. A mixed-methods study showed that adolescents may experience a decrement in health-related quality of life in response to adverse cholesterol screening results, underlining the importance of focusing screening on conditions with significant health impact and effective interventions (eg, FH), vs lifestyle-related dyslipidemias with a small response to lifestyle interventions. Pooled US childhood cohort data support the idea that 9 years is a good age for screening for FH. This is because LDL-C values at this age are most similar to young adult LDL-C values and because the separation between LDL-C distributions in individuals with FH-causative variants and individuals without FH-causative variants is greatest at this age. Economic evaluations can guide uptake at scale, particularly if they include implementation costs and long-term outcomes. There are some economic data on the use of genetic testing to identify FH in US adults, in children outside the US, and on cascade FH screening in adults, and there is 1 recent cost analysis of childhood universal vs targeted lipid screening for hyperlipidemia; however, there are no cost-effectiveness analyses of lipid-based screening for FH in children assessing downstream health outcomes. Cost-effectiveness of childhood lipid screening is likely to vary by disease targeted (primary vs secondary lipid disorders), disease prevalence in the population, and the cost of testing and follow-up. Research to bridge the knowledge gaps identified by the USPSTF will likely require novel and pragmatic study designs to allow for the large sample size and long-term follow-up needed to address questions related to long-term effectiveness and safety of treatments.

While the evidence gaps are being filled—and it is imperative that they are—the current I statement from the USPSTF leaves a void for clinicians seeking to provide care for their patients today. Clinicians may consider existing guidance from the American Academy of Pediatrics recommending universal childhood lipid screening at ages 9 to 11 years and again at ages 17 to 21 years, and guidance from the American Heart Association and American College of Cardiology recommending childhood lipid screening at the same ages (a class IIb recommendation). If lipid testing yields very high lipid levels, particularly if there is a family history of early ischemic heart disease, clinicians should consider genetic testing for FH, specifically to identify homozygous FH. If FH is identified, cascade testing of first- and second-degree relatives may help diagnose additional cases, including adults at more proximal risk for premature coronary disease meeting current treatment guidelines. Lifestyle modification counseling and lipid-lowering therapy including statins should be offered to people diagnosed with FH, based on good-quality, short- to medium-term data showing favorable safety and lipid-lowering effect. Clinicians should also evaluate and treat their pediatric and adolescent patients at high risk for secondary lipid disorders and premature atherosclerotic cardiovascular disease based on existing clinical guidance.

The current I statement from the USPSTF pushes the possibility of a systematic national childhood lipid screening program into the future. However, we believe that the evidence supporting specific screening for and treatment of FH in childhood is growing, and a universal screening approach to reduce the burden of premature atherosclerotic cardiovascular disease among persons with FH will likely be adopted in the future. In the meantime, clinicians can rely on existing guidelines and decide together with pediatric patients and their families if and when to screen for lipid disorders in childhood.

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