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Counterpoint: The evidence does not support universal screening and treatment in children

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Abstract: Few pediatric guidelines have generated the amount or intensity of controversy that the pediatric lipid guidelines have. In the following article, I will synthesize the arguments against universal lipid screening and treatment in childhood. Direct evidence that relates the presence of cardiovascular risk factors in childhood to cardiovascular disease outcomes in adulthood is unavailable, and as a consequence, the guidelines were formulated based on a chain of indirect evidence. The debate centers on the strength of the indirect evidence that links risk factors present in childhood to adult disease outcomes. The arguments against universal lipid screening and treatment of children include (1) a history of unanticipated harms caused by screening tests or treatments that were enacted based on indirect evidence, (2) the poor test performance characteristics of lipid profiles in childhood when used as a screening test, (3) problems with the effectiveness of lipid testing done in the office setting, and (4) concerns regarding the safety of statins when used in children.

Lessons from screening programs enacted in the absence of direct outcomes

An overarching concern regarding lipid screening in childhood is the absence of long-term adult outcome data. Early detection leading to earlier treatment does not always improve patient outcomes. For example, screening infants for neuroblastoma does not improve prognosis[1] and also leads to the harmful overtreatment of tumors that regress spontaneously.[2] Similarly, the Unites States Preventive Services Task Force's (USPSTF) review of the utility of prostate-specific antigen screening in asymptomatic men clearly established that screening resulted in the overtly harmful overtreatment of countless men for asymptomatic cancers that would not have progressed to an illness.[3] A similar phenomenon of overdiagnosis has been hypothesized to be occurring currently in Korea where increased ultrasound-based thyroid cancer screening has created an epidemic of cancer prevalence that is not associated with a change in mortality rates from the condition.[4]

The unanticipated harms of using medications in the absence of rigorous trials to establish a net benefit on disease outcomes were highlighted by the Women's Health Initiative trial.[5] The trial was based on aggregated observational data and on surrogate outcomes that suggested a cardioprotective effect of postmenopausal hormone use in women. It was stopped early because of an increase of breast cancer among women in the active arm of the trial who, despite favorable changes in their lipid profiles, also

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had greater numbers of coronary heart disease events and stroke than those in the controls.[5] In this regard, it is also interesting to consider that an absence of the highest level of direct evidence of net benefit is cited in the 2013 American College of Cardiology/American Heart Association guideline as the reason that adults aged younger than 40 years without heart disease or diabetes and with a low-density lipoprotein cholesterol (LDL-C) of <190 mg/dL would not qualify for statins based on risk scoring. To quote directly from the guideline document, "treatment strategies based on lifetime atherosclerotic cardiovascular disease (ASCVD) risk are problematic because of the lack of data on the long-term follow-up of randomized controlled trials (RCTs) >15 years, the safety and ASCVD event reduction when statins are used for periods >10 years, and treatment of individuals <40 years of age."[6] Thus, it has been estimated that as many as 400,000 young adults transitioning to adult care whose pediatrician would have prescribed statins based on the National Heart, Blood, and Lung Institute (NHLBI) 2011 guideline would then have their statins discontinued by their internist for lack of direct evidence of efficacy of this approach in adulthood.[7]

Atherosclerosis does not always progress to a clinical illness and consequently both cardiovascular risk factors and surrogate markers of atherosclerosis are vulnerable to overdiagnosis. In addition, there is a need for longer term rigorous data to support the use of statins beginning in childhood. Internists are aware of the harms of overdiagnosis,[8] and pediatricians are becoming increasingly aware of this concept[9] that is highly relevant to pediatric lipid screening.

Performance characteristics of the pediatric guidelines

The effectiveness of the current lipid screening guidelines to directly predict adult atherosclerotic cardiovascular disease outcomes is untested. The effectiveness of the current guidelines to predict which children would go on to become adults with risk scores at age 40 years for whom statins would be recommended is also unstudied and unknown. However, whether abnormal lipid values obtained during childhood persist over time, a phenomenon known as tracking, has been imputed from observational cohort studies. On the basis of an analysis of 23 studies, the 2007 USPSTF summary report on lipid screening in childhood concluded that tracking of lipids over the course of 4 to 15 years was 40% to 55%.[10]

The landmark Princeton Lipid Research Prevalence Program Follow-Up Study examined the diagnostic utility of lipids measured in a cohort of 5- to 19-year olds followed to ages 28 to 48 years.[11] The results of this study figured prominently in the 2011 NHLBI guidelines. Overall, for the entire cohort, the sensitivity and specificity of childhood LDL-C of ≥130 mg/dL to predict an adult LDL-C of ≥160 mg/dL was 46% and 86%, respectively. The positive predictive value was 39% and the negative predictive value was 88%. These values were noted to be highly age dependent. The sensitivities and specificities of elevated childhood LDL-C to predict an elevated adult LDL-C for the age ranges at which the NHLBI panel chose to recommend universal lipid screening, 9 to 11, and 17 to 21[12] are not possible to derive precisely from the Princeton Lipid Research Follow-Up Study. However, using age-specific point estimates from a published figure, it appears that sensitivities vary from a low value of 26% at age 11 years to a high value of 69% at age 9 years. The specificity ranges from a low value of 78% at age 11 years to a high value of 92% at age 10 years.[11] Thus, lipid screening would miss up to 74% of individuals who are screened at age 11 years and would also incorrectly label 22% of 11-year olds as being at high future risk.[13] Whether these values are an acceptable basis for a screening test is debatable.

The Princeton study[11] and other large population-based studies have noted significant effects of age, gender, and race on lipid levels throughout childhood posing a further significant challenge to the performance characteristics of a childhood screening paradigm that relies on a single cutpoint for non–high-density lipoprotein cholesterol (non–HDL-C) values and LDL-C values irrespective of gender and race. The strong possibility that the NHLBI-recommended lipid-testing scheme could differentially misclassify children based on their race and engender disparities needs to be explicitly tested especially in light of the fact that prior iterations of the lipid guidelines resulted in racial disparities.[13]

Apart from a concern with the level of false negative tests for the prediction of adult LDL-C, there is also concern over the large numbers of true negatives for adult lipid risk who are in fact false negatives for adult cardiovascular disease outcomes.[14,15] The cholesterol-centric testing paradigm has the potential unintended consequence of reassuring the families of obese children who in fact are most of the individuals at future cardiovascular risk.[16,17] Whether millions of families of obese children would be demotivated by virtue of being informed that their child's LDL-C value is in a low-risk range is an unknown and an unstudied harm. In one study of obese adolescents studied retrospectively following an office visit in which cholesterol screening was done, there was no associated benefit in body mass index status when compared with those who were not screened.[18]

The effectiveness of the screening guidelines

The effectiveness of the current guidelines to identify and improve cardiovascular risk profiles in children has not been directly tested. The provision that children can be screened in the nonfasting state and then progress to 2