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Changing the Conversation Regarding Pediatric Cholesterol Screening:

The Rare Disease Paradigm

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In a debate at a meeting of the Pediatric Academic Societies in May 2012, I reiterated arguments against universal pediatric lipid screening because instituting the 2011 National Heart, Lung, and Blood Institute Expert Panel recommendations would identify a huge number of children who will never get heart disease, would require large amounts of resources, and would inflict torment on providers and patients for precious little return.[1] During the ensuing discussion period, up to the microphone walked a 30-year-old woman who related her unexpected myocardial infarction some 5 years ago. Her poignant narrative reminded me of the first patient that I ever saw when I was a bright-eyed intern in the emergency department. He was 31 years old and had been dropped off by his wife for “ear pain” on her way to work. A few minutes later, he had a cardiac arrest and could not be resuscitated. These cases spotlight our dilemma regarding cardiovascular risk prevention starting early in life. How can we prevent these unanticipated cases of serious, sometimes fatal ischemic heart disease in young adults without weighing down an entire pediatric care system?

The rhetoric supporting widespread pediatric lipid screening, as well as screening for other cardiovascular disease risk factors in youth, typically begins with recounting the burden of cardiovascular disease in our society. It is the number one killer in the United States and will soon be so throughout the world. We need to prevent it, beginning in childhood when the atherosclerotic process starts. But it does not necessarily follow that lipid screening is a good way to achieve this laudable goal.[1] First, population-based approaches are likely to be more effective and cost-effective, especially those that use policy or environmental strategies. Even in the face of the obesity epidemic, for example, lipid levels in the United States have actually improved over the past decade. This trend likely owes at least as much to the

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reduction of *trans* fats in the US food supply than to anything clinicians can do. Second, for the large majority of "affected" children whose low-density lipoprotein cholesterol (LDL-C) levels are modestly elevated, waiting until adulthood to treat is a better strategy because these patients will not experience heart disease in early adulthood and otherwise would have to suffer decades of labeling, futile efforts at behavior change, and, for the few who are prescribed drugs, mounting adverse effects of long-term treatment. Furthermore, for those who aver that screening will change behavior, the evidence is scarce that "knowing your number" is an effective strategy for children and adolescents, and the results are mixed for adults. Moreover, which behavior to change is nebulous. Hypertriglyceridemia, which accompanies obesity, responds to modest weight loss and carbohydrate reduction, but it is not a strong cardiovascular risk factor. Low-density lipoprotein cholesterol, which is more weakly associated with obesity but strongly associated with risk of heart disease, hardly responds even to resource-intensive lifestyle intervention.

In contrast to the rationale for cardiovascular risk factors, the goal of pediatric screening for other diseases—primarily in the newborn period—is not to reduce the burden of a common disorder but to identify and mitigate adverse outcomes for rare but serious conditions. For example, all states mandate screening for congenital hypothyroidism, which occurs in about 1 in 4000 births, cystic fibrosis (1 in 2500 whites), and sickle cell anemia (1 in 400 African Americans). The analogy in cardiovascular disease is familial hypercholesterolemia, an autosomal dominant condition characterized by LDL receptor deficiency or abnormality, the heterozygous form of which occurs in 1 in 500 individuals. Before the statin era, this condition was associated with a cumulative incidence of ischemic heart disease events of about 1 in 6 men and 1 in 10 women by the age of 40 years, yielding population cumulative incidences similar to these other "rare diseases": 1 in 3000 for men (1/500 × 1/6) and 1 in 5000 for women (1/500 × 1/10). By the age of 60 years, these frequencies increased to 1 in 1000 for men and 1 in 1500 for women.[2] Given the frequency of this condition, its somber prognosis, and the promising results from short-term randomized controlled trials of statin therapy, it makes sense to identify and treat adolescents with familial hypercholesterolemia.

By analogy with the newborn screening tests, the way to detect familial hypercholesterolemia without netting a large number of children with only moderate LDL-C elevations is to set the cut point of the screening test very high. In the 1970s, Leonard et al[3] demonstrated that a single total cholesterol measurement above 270 mg/dL or below 252 mg/dL (to convert to millimoles per liter, multiply by 0.0259) distinguished affected from nonaffected children quite well. Repeated measures would narrow the zone of uncertainty. A total cholesterol level of 270 mg/dL translates to an LDL-C level of near 180 mg/dL, which is much higher than the currently recommended cut point for further workup and treatment of 130 mg/dL. Combining a high cut point with family history, physical findings, and/or genetic testing appears to the yield the most accurate diagnosis.[4]

Research is needed to determine if this "rare disease" screening approach is the correct one and, if so, how to implement it. First, studies are needed of current screening practices among clinicians and families, and of their attitudes toward accepting this new paradigm. Second, long-term randomized trials of pediatric screening with adult clinical end points are infeasible, but shorter-term trials to compare effects of universal vs state-of-the-art selective

screening on surrogate outcomes, with varying cut points, would be invaluable. Third, simulation models incorporating long-term outcomes are the best way to analyze multiple scenarios. In a model of blood pressure screening in youth, for example, population-based approaches to reduce salt intake and increase the frequency of physical education classes were both more effective and less costly than any screening-based approaches.[5] Considering only screening-based approaches, we found that the most cost-effective strategy was analogous to detecting familial hypercholesterolemia in lipid screening: identify and treat only those at the very highest risk—that is, adolescents with secondary causes for hypertension or end-organ damage such as left ventricular hypertrophy.[5] In Europe, it appears that cascade (family tracing) screening for familial hypercholesterolemia is more cost-effective than universal screening.[4] Objective and transparent approaches for integrating all of these strands of research will be critical for future guideline revisions.

Since the release of the National Heart, Lung, and Blood Institute Expert Panel guidelines almost 16 year ago, vitriol around lipid screening has permeated discussions and published commentaries. Changing the screening perspective from common to rare disease may very well promote equanimity and, more importantly, improved recommendations for cardiovascular risk factor screening in youth. Pairing public health approaches for reducing the overall burden of cardiovascular disease with screening to detect and treat only the most severely affected adolescents is likely to be the winning combination.

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