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Cholesterol Screening in Children: Is a Universal Approach Working?

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Abstract
Purpose of Review: Ample evidence supports that an individual's lifetime risk of atherosclerotic cardiovascular disease correlates to long-term, cumulative exposure to circulating cholesterol levels, beginning in childhood. Selective screening strategies based on family history fail to identify many children with hypercholesterolemia. Universal cholesterol screening in childhood is a worthwhile goal. However, cholesterol screening rates through childhood remain low.
Recent Findings: Mounting evidence clarifies the barriers to cholesterol screening in children. Specific strategies to foster universal screening in childhood have been proposed.
Summary: We present an overview of the present state of childhood cholesterol screening, summarizing historical and contemporary guidelines and collating evidence of low adherence to current guidelines. We contend that novel approaches to universal cholesterol screening in childhood are warranted, and we present potential opportunities for improvement. We call for new and universal pediatric cholesterol screening guidelines.

Keywords barriers · cholesterol · dyslipidemia · hypercholesterolemia · pediatric · screening

Introduction

Atherosclerotic Cardiovascular Disease (ASCVD) remains among the leading causes of death in the United States (U.S.) [1]. In 2019 alone, excluding heart failure, hospitalizations in the U.S. for coronary atherosclerosis or acute myocardial infarction cost over $112.8 billion [2]. In a search for etiologies, the Framingham Heart research group found, in 1961, that high blood cholesterol levels were associated with an increased likelihood of coronary artery disease [3]. Over 55 years later, the European Atherosclerosis Society became the first major professional society to declare that cumulative exposure to low-density lipoprotein cholesterol (LDL-C) *causes* ASCVD. The group noted that "long-term exposure to lower LDL-C is associated with up to a three-fold greater proportional reduction in the risk of cardiovascular disease per unit reduction in LDL-C, when compared with shorter-term treatment with a statin started later in life after atherosclerosis has developed" [4]. That observation provides adequate justification for "primordial prevention" of atherosclerosis. Stary identified "advanced" atherosclerotic lesions of the coronary arteries of nearly 10% of general population 12-14-year-olds [5]. However, there is compelling evidence that, when LDL-C levels are exceptionally high, atherosclerosis is even more prevalent at younger ages [6].

Among the causes of moderate-to-severe hypercholesterolemia are several monogenic disorders [7]. At an estimated prevalence among U.S. adolescents of 1:237, the most common is inherited co-dominantly and known as Familial Hypercholesterolemia (FH) [8]. If untreated, the significantly elevated LDL-C levels of patients with FH predispose them to a much higher—and much expedited—risk of major adverse cardiovascular events (MACE) compared to the general population [9–16]. Worse subclinical vascular health has even been shown among heterozygous FH populations (versus non-FH siblings) among children under 8 years old [17].

FH is, however, treatable, and there is an expanding array of options available for children with hypercholesterolemia. In recent years, the U.S. Food and Drug Administration has approved the use, by children, of pitavastatin (2019), evolocumab (2021), and evinacumab (2021, updated 2023). According to ClinicalTrials.gov, prospective pediatric trials of lomitapide or inclisiran are ongoing. While data on the

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long-term risks and benefits of newer drugs being initiated in childhood have not yet been published, 20-year follow-up data on pravastatin usage by heterozygous FH patients beginning in middle childhood have been encouraging [18]. The American Heart Association has endorsed the use of statins in children with heterozygous FH as young as 8-10 years old [19, 20]. Statin initiation in adulthood has not yet eliminated the excess event risk of FH, making early detection and treatment of FH highly important [9–11]. Whether newer lipid-lowering drugs or combination therapies, initiated in adulthood, will mitigate the excess risk of FH remains unknown. However, the cost of such approaches often limits their use in primary and secondary prevention. Early detection and treatment of FH, starting in childhood, may significantly reduce the need for more costly and aggressive lipid-lowering therapy in adulthood. It is estimated that only 31.1% of those with FH have been identified in the U.S., and the rate of FH identification remains poor worldwide [21••].

As the most prevalent single-gene disorder in humans—causing substantial, yet easily mitigatable, hazards—FH has long attracted interest as a target for screening [22]. In 1989, the American Academy of Pediatrics (AAP) proposed expanding selective pediatric cholesterol screening to the clinical realm—a notion soon clarified and championed by the National Cholesterol Education Program (NCEP) [23, 24]. In 2011, the National Heart, Lung, and Blood Institute (NHLBI) presented a more ambitious proposal: that *universal* screening of U.S. youth should occur at 9-11 years old [25], in addition to selective screening at other ages based on risk factors. The NHLBI guideline was embraced by the AAP, as well as many other U.S. professional societies. We summarize existing guidelines for pediatric cholesterol screening in Table 1. However, the NHLBI's recommendation for universal cholesterol screening in childhood has not been widely accepted or integrated into routine clinical practice. A review of over 60,000 well-child visits from three large datasets demonstrated no overall change in the rate of cholesterol screening among children 9-11 years old after the release of the 2011 NHLBI guidelines [31]. As says the U.S. Preventive Services Task Force (USPSTF), "Recent studies investigating screening practices in large U.S. health care organizations have found universal screening rates of 2 to 9 percent in children between 9 and 11 years of age" [26]. Troublingly, missed cholesterol screenings *often* have been intentional. In two recent surveys of U.S. pediatricians, nearly half of the respondents reported regularly omitting screening patients for hypercholesterolemia, believing that universal cholesterol screening is "not appropriate" [32, 33]. The Lown Institute's Right Care Alliance Children's Health Council has even ranked routine cholesterol screenings among their "top five 'don't' recommendations" for child healthcare [34]. In this review, we examine what is currently known about the beliefs and practices of healthcare providers regarding the potential benefits/limitations/harms of universal cholesterol screening in childhood (Table 2). We also propose ways of increasing such screening rates to improve healthcare outcomes for youth at risk for premature cardiovascular disease (Table 3).

Barriers & Solutions

A Misperception that Targeted Screening is Sufficient to Identify at-risk Children

The presence of obesity, chronic kidney disease, Kawasaki disease, Human Immunodeficiency Virus infection, cardiomyopathy, an endocrinopathy, or a transplanted heart has been shown to correlate with a higher likelihood of a child undergoing cholesterol screening [35–38]. Although many of those factors are important causes of hyperlipidemia among children, FH exists independent of those factors, thus sneaking "under the radar" despite its insidious harm.

In 1991, the NCEP proposed principally family-history-based criteria for screening children selectively for hypercholesterolemia in clinical practice [24]. It is conceivable that many healthcare professionals mistake the now-antiquated NCEP guideline as a current care standard. That such a misunderstanding may exist is suggested by a recent national survey having found that 30% of pediatricians felt that a review of family history is "sufficient to identify familial dyslipidemias" [33]. Moreover, in a survey of family physicians, most respondents reported screening pediatric patients for hypercholesterolemia only *selectively*, with a family history of hypercholesterolemia, heart attack, or stroke among the biggest measured influencers favoring screening [39].

Unfortunately, in practice, family histories are often incompletely known. The demonstrated consequence is that selective pediatric cholesterol screening approaches that rely on family history miss a vital share of children with hypercholesterolemia [40–42]. In the U.S., just 2 in 5 young adults—the demographic that predominates as parents to young children—self-report having undergone a cholesterol screening in the preceding 5 years. Moreover, only 1 in 5 young adults in the U.S. who have hypercholesterolemia have awareness of their hypercholesterolemia [43]. Such numbers strongly suggest an implementation problem under a paradigm of family-history-driven selective pediatric cholesterol screening. "Cascade screening" refers to the practice of screening for a given disease the relatives (usually progeny) of those diagnosed with the disease. Though efforts to understand and deepen family tracing in cascade-based cholesterol screening approaches, including outreach to ask adult specialists to promote cholesterol screening

Table 1 Overview of select major U.S. pediatric cholesterol screening guidelines for all populations

Year	Issuing Body	Approach	Criteria	Reference
2023	U.S. Preventive Services Task Force	N/A	"The evidence is insufficient, and the balance of benefits and harms for screening for lipid disorders in asymptomatic children and adolescents age 20 years or younger cannot be determined."	[26]
2018	The "Multi-Society" guidelines: American College of Cardiology / American Heart Association (AHA) / American Association of Cardiovascular and Pulmonary Rehabilitation / American Academy of Physician Assistants / Association of Black Cardiologists / American College of Preventive Medicine / American Diabetes Association / American Geriatrics Society / American Pharmacists Association / American Society for Preventive Cardiology / National Lipid Association / Preventive Cardiovascular Nurses Association	Ambiguous	Beginning at 2 years old, selective hypercholesterolemia screening in childhood is encouraged if a patient's siblings, parents, aunts/uncles, or grandparents had either early ASCVD or significant primary hypercholesterolemia. Universal cholesterol screening—once between 9 and 11 years of age and once more between 17 and 21 years of age—"may be reasonable." Such screening may be conducted via a fasting lipid profile or a non-fasting non-HDL-C level.	[19]
2017	American Association of Clinical Endocrinologists (AACE) / American College of Endocrinology	Universal	In children whose brother or father has a history of definite myocardial infarction or sudden death < 55 years of age or whose sister or mother has a history of definite myocardial infarction or sudden death < 65 years of age, or when there is a family history of cholesterol levels consistent with FH, hypercholesterolemia screening should be undertaken when the child is 3 years of age, again between ages 9 and 11, and again at age 18. Patients ≥ 16 years old should be screened for hypercholesterolemia every 5 years—or more frequently if the patient has ASCVD risk factors, is overweight or obese, has other elements of the insulin resistance syndrome, or has a family history of premature ASCVD. Universal screening may be reasonable. "The AACE endorses current AAP, AHA, NHLBI, and NLA recommendations and position statements for targeted and universal dyslipidemia screening in children and adolescents."	[27]
2016	U.S. Preventive Services Task Force	N/A	"The current evidence is insufficient to assess the balance of benefits and harms of screening for lipid disorders in children and adolescents 20 years or younger."	[28]*
2015	National Lipid Association (NLA)	Universal	Selective screening for hypercholesterolemia should begin at 2 years old when children have at least one parent with hypercholesterolemia or who is receiving lipid-lowering medications, or when an expanded first-degree pedigree reveals a family history of males with ASCVD < 55 years old or of females with ASCVD < 65 years old, or when family history is unknown. All children 9−11 years old should be screened once for hypercholesterolemia within that window and again at 20 years of age. Screening samples may be obtained via fingerstick or venipuncture and testing may be performed via a non-fasting non-HDL-C measurement.	[29]
2014	American Academy of Pediatrics' Bright Futures program	Universal	For children 2 or 4 or 6 or 8 years old, check a fasting lipid profile × 2 **if**: (1) a parent has had a total cholesterol of ≥ 240 mg/dL or a known dyslipidemia; (2) a sibling, parent, aunt/uncle, or grandparent has had—at < 55 years old among males or at < 65 years old among females—a myocardial infarction, angina, stroke, or procedure-treated atherosclerotic coronary artery disease; OR (3) the child smokes cigarettes or has diabetes, hypertension, obesity, chronic kidney disease, a transplanted heart or kidney, Human Immunodeficiency Virus infection, a chronic inflammatory disease (such as lupus or rheumatoid arthritis), or any history of coronary artery aneurysm related to Kawasaki disease. For **all** patients 9-21 years old, follow the AAP-endorsed guidance as issued from the NHLBI.	[30]

Table 1 (continued)

Year	Issuing Body	Approach	Criteria	Reference
2011	National Institutes of Health's National Heart Lung, and Blood Institute (NHLBI)	Universal	For children 2-8 years old, check a fasting lipid profile × 2 **if**: (1) a parent has had a total cholesterol of ≥ 240 mg/dL or a known dyslipidemia; (2) a sibling, parent, aunt/uncle, or grandparent has had—at < 55 years old among males or at < 65 years old among females—a myocardial infarction, angina, stroke, or procedure-treated atherosclerotic coronary artery disease; OR (3) the child smokes cigarettes or has diabetes, hypertension, obesity, chronic kidney disease, a transplanted heart or kidney, Human Immunodeficiency Virus infection, a chronic inflammatory disease (such as lupus or rheumatoid arthritis), or any history of coronary artery aneurysm related to Kawasaki disease. For **all** children 9−11 years old, check a non-fasting non-HDL-C level or a fasting lipid profile. For children 12−16 years old, check a fasting lipid profile × 2 **if** there is "new knowledge" of: (1) a parent having had a total cholesterol of ≥ 240 mg/dL or a known dyslipidemia; (2) a sibling, parent, aunt/uncle, or grandparent having had—at < 55 years old among males or at < 65 years old among females—a myocardial infarction, angina, stroke, sudden cardiac death, or procedure-treated atherosclerotic coronary artery disease; OR (3) the child smokes cigarettes or has diabetes, hypertension, overweight, chronic kidney disease, a transplanted heart or kidney, Human Immunodeficiency Virus infection, a chronic inflammatory disease (such as lupus or rheumatoid arthritis), or any history of coronary artery aneurysm related to Kawasaki disease. For **all** patients 17−21 years old, check a non-fasting non-HDL-C level or a fasting lipid profile.	[25]
1991	National Institute of Health's National Cholesterol Education Panel	Selective	At any age beyond 2 years old, a non-fasting total cholesterol level should be measured in the children of all parents whose total cholesterol level had ever been ≥ 240 mg/dL. (The NCEP acknowledged that even perfect application of that parental threshold would detect only about 40% of children with LDL-C levels of ≥ 130 mg/dL.) The NCEP *also* recommended that a fasting full lipid profile should be sought for children whose parent or grandparent—at ≤ 55 years old—had had myocardial infarction, angina, peripheral vascular disease, cerebrovascular disease, sudden cardiac death, or angiographically-demonstrated coronary artery disease; or—optionally—if parental or grandparental medical history were unobtainable or if other risk factors for ASCVD had been identified in the child. Lastly, the NCEP recommended lipid re-screening for any child still eligible for screening every 5 years.	[24]
1989	American Academy of Pediatrics' Committee on Nutrition	Selective	Regular elective testing (a fasting lipid profile and lipoprotein levels) of children > 2 years of age who have a sibling, parent, aunt/uncle, or grandparent of hyperlipidemia or— < 50 years of age in males or < 60 years of age in females—of atherosclerotic coronary artery disease / myocardial infarction.	[23]

*Also see https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/lipid-disorders-in-children-screening-july-2016

Table 2 Why Universal Pediatric Hypercholesterolemia Screening?

Reasons to Screen
• Familial hypercholesterolemia is the most common monogenic disease in humankind
• Readily available treatments for Familial Hypercholesterolemia significantly lower the morbidity and mortality of the disease
• Consensus exists regarding which hypercholesterolemic patients require treatment and the targets and biochemical goals of care
• Familial Hypercholesterolemia is identifiable in an asymptomatic phase by widely available screens that are acceptable to the public and inexpensive relative to the cost of the undetected disease.

of the children of their hypercholesterolemic patients may usefully boost identification of pediatric FH, the USPSTF has noted that "rigorous cascade screening is not currently implementable in the United States due to HIPAA and lack of current infrastructure" [26, 44–49]. Moreover, population health modeling demonstrates that "Cascade testing is not [*alone*] a suitable method of population screening for FH, because a separate method of systematically identifying new FH index cases is required to achieve a reasonable level of FH detection in the population" [50].

The cost-effectiveness of universal versus selective cholesterol screening remains a topic of active debate. Proponents of biochemical cascade screening for FH may cite studies demonstrating that such screening can be cost-effective in the U.S. [51]. However, one recent pediatric-testing model contends that 126,000 *extra* 10-year-olds per year in the U.S. would be diagnosed with hyperlipidemia (including 8,000 *extra* children diagnosed with severe hypercholesterolemia, 7,000 of whom promptly would qualify for a lipid-lowering prescription) utilizing a strategy of universal, versus selective, screening. The cost per diet-refractory severe hypercholesterolemia case detected predictably rises with universal, versus selective, cholesterol testing. However, it increases only to $12,590 per case identified through universal screening—a meager expense compared to the decades of cost spent on individuals with ASCVD [52].

Guideline-Based Barriers

Much of the divide between proponents and opponents of universal childhood cholesterol screening falls along medical specialty lines. Compared to pediatricians, family practitioners more often oppose universal childhood cholesterol screening [39]. That difference may be due substantially to perceived conflicts amongst competing professional society traditions, philosophies of care, and guidelines [53]. While the American Academy of Pediatrics leans toward an activist *modus operandi*, the American Academy of Family Physicians openly acknowledges hewing closely on medical policy matters to the clinical assessments of the conservative USPSTF. Indeed, in regard to the concept of pediatric cholesterol screenings, the website of the American Academy of Family Physicians (AAFP) explicitly states that "The AAFP supports … USPSTF… recommendations on this topic" [54]. However, although the USPSTF has released several meticulously-curated evidence reviews on pediatric cholesterol screenings, no summary statement from the USPSTF officially contains any actual recommendation on the subject. Its most recent "final" assessment, from 2016, and its just-published draft-released evidence review both state that there is "insufficient evidence" for the USPSTF to issue any practice recommendation, perpetuating ambiguity

Table 3 Cholesterol Screening in Youth: Barriers & Opportunities

Barriers	Opportunities
• Misconception that targeted and/or cascade screening is adequately sensitive to identify at-risk children	• Simplify cholesterol screening interpretation and specialist referral criteria
• Incomplete/inaccurate family histories	• Broaden non-fasting cholesterol screening
• Discordant, complex, and misunderstood "consensus" childhood cholesterol screening guidelines	• Point-of-care cholesterol screening
• Limited specificity of guideline-endorsed cutpoints for "positive" childhood cholesterol screenings	• Raise the recommended thresholds for defining a cholesterol screening as "positive"
• PCP inexperience and discomfort with interpretation of multi-valued lipid panels for children	• "Piggyback" cholesterol screening with other necessary needlesticks
• Coordination of fasting and/or laboratory-based screening poses logistical challenges	• Retarget cholesterol screening to the age when differentiation between genetically vs. lifestyle-mediated hypercholesterolemia is most robust
• Dedicated blood draw(s) *de facto* required under current pediatric cholesterol screening guidelines	• Educational initiatives to PCPs
• Competing, and often more pressing, preventive and social care priorities	• Improve policies surrounding reimbursement for cholesterol screening
• Primary care inexperience in managing pediatric dyslipidemia (e.g. dietary counseling)	
• Limited access to lipidologists	
• Misperception of hypercholesterolemia treatment risks	
• Gaps in insurance coverage	

about how—or even whether—the AAFP endorses cholesterol screening should proceed in the pediatric population [26, 28]. Some sources have misinterpreted the USPSTF's most recent final determination as advising *against* pediatric cholesterol screenings [55]. At the least, many family practitioners have interpreted the USPSTF's ambivalence as extending permission to direct their attention toward other medical issues. However, such an approach yields noticeably narrower testing guidance across the hypercholesterolemia care age spectrum [56].

In some data sets, cholesterol screening rates among children 9-11 years old declined following the release of the USPSTF's 2016 statement on pediatric lipid screening [53]. That has been tragic for patients whose FH has gone undetected and whose lives may be shortened by decades—and that pattern likely will repeat in the aftermath of the USPSTF's meticulous, but misguided, 2023 literature summary. A June 22, 2023 Medline search for ((pediatr$ or children) and (cholesterol or lipid or dyslipid$ or hyperlipid$ or hypercholesterol$) and (screening or detecting or identification or finding or sensitiv$)).ti,ab.—excluding review and non-English articles—returned 2,363 articles. However, in their recently released 314 page report on pediatric cholesterol screening, the USPSTF report's authors—only one of whom is a physician—found *no* study adequate to address either of its self-framed "Key Questions" containing the word "screening." Most troublingly, as others have suggested of past USPSTF statements, the USPSTF's Key Questions on childhood cholesterol screening are inveterately unanswerable *practically* [57–61].

In its latest iteration, the USPSTF asks whether screening children for FH or multifactorial dyslipidemia delays or reduces the incidence of health outcomes or improves intermediate outcomes [26]. To satisfy such an inquiry for FH, a prospective trial would need to cholesterol-screen >12,000 U.S. ten-year-olds (to find 50 with FH at a 1:237 prevalence) and >>12,000 previously-unscreened U.S. twenty-year-olds (necessitating >>13,000 chart reviews, assuming a 9% cholesterol screening rate among ten-year-olds) to find 50 with FH, follow for a decade the subjects enrolling at ten years old, and compare differences in the carotid intimal-medial thickness (CIMT) between the two groups at twenty years old. Alternatively, one could scour the medical records of 133,000 U.S. twenty-year-olds to find 50 who were diagnosed biochemically with FH at ten years old (assuming a 1:237 FH prevalence, discovered at a 9% screening rate) plus >>12,000 U.S. twenty-year-olds who were not screened for hypercholesterolemia at ten years old (again necessitating >>13,000 chart reviews). Those >>12,000 twenty-year-olds would need to be screened for FH (~50 of whom will, in fact, have had FH all along). CIMT could then be compared between the two groups. Because of the higher prevalence of multifactorial dyslipidemia, smaller, but analogous, studies could be undertaken in pursuit of a justification for childhood lipid screening. However, given multifactorial dyslipidemia's more modest hypercholesterolemia, a clinically-meaningful difference between groups might be harder to demonstrate. Moreover, valid objections could be raised that the subjects first identified as having multifactorial dyslipidemia at twenty years old might not have had stable multifactorial dyslipidemia since they were ten years old. In practice, then, it is highly unlikely that any of those studies ever will be done. Like a hamster in its cage, the USPSTF spins its wheel perpetually, while getting nowhere. The USPSTF is apparently satisfied with that outcome, but we—family practitioners included—should not be. The rubber can reach the road by a different tact, such as a systematic application of evidence on pediatric cholesterol screening to Wilson and Jungner's classic screening principles [62].

The length and complexity of guidelines and test interpretation can also hinder guideline adoption. What was asked of the primary care community in the official *summary* figures for the 2011 NHLBI recommendations spanned one-and-a-half daunting journal pages, failed to define separately primary care and subspecialist roles in pediatric cholesterol screening and care, and encouraged *two* fasting lipid profiles prior to intervention [25]. In a survey, one-third of pediatricians admitted a lack of comfort with interpreting a lipid profile, citing that as a barrier to screening. Additionally, 90% noted that the need for *fasting* discourages cholesterol screening [33]. Some also report that achieving comprehensively the tasks recommended within the ever-growing AAP's Bright Futures' periodicity schedule is unrealistically ambitious in the limited time that practices allot to well visits—obliging omissions [63–65]. A primary care physician commented to one of the authors of this paper (TCD) that he felt it necessary to concentrate well-child care "on what might kill…[his] patients in the next year." Viewed through that lens, childhood cholesterol screening may register to primary care providers (PCPs) as a low priority even when they endorse hypercholesterolemia's long-term public health significance [33, 39, 66••, 67].

While the reasons for patient and parent refusals of blood collections have not been explored academically, traditional venipuncture requires painful needle sticks, and most children and 20-50% of adolescents fear needles—an understandable barrier to cholesterol screening efforts [68, 69]. No other laboratory blood testing routinely is recommended by the AAP for patients anywhere close to 9-11 years old. Last, but not least, PCPs also report reluctance to inconvenience their patients to seek cholesterol care from subspecialists when the current NHLBI-guideline-recommended lipid level threshold for further investigation (non-HDL ≥145 mg/dL) affords only 38% specificity in the identification of patients who require prescription pharmacotherapy [70, 71]. Indeed, half of the pediatricians responding to one survey "agreed

or strongly agreed that 'screening all children for high cholesterol will lead to unnecessary and costly follow-up'" [33].

Guidelines-Based Solutions

Sensible solutions do exist, and there is growing evidence of their efficacy. Multiple studies have shown practical equivalency between fasting and nonfasting clinical cholesterol level results for initial screening [72–75]. It is uncommon for hypertriglyceridemia to interfere seriously with hypercholesterolemia care at the screening and diagnostic stages [76–79]. Even in the rare instance when hypertriglyceridemia is marked, new formulas for calculating LDL-C levels are helping to sharpen what diagnostic insights may still be gleaned [80, 81]. Given what is known about nonfasting cholesterol screening, the 2018 "multisociety" guidelines on cholesterol explicitly state, "Nonfasting lipid parameters are similar to fasting ones, and screening with a nonfasting non–HDL-C is a reasonable approach to population screening in childhood" [19].

Explicit encouragement of point-of-care testing in support of childhood cholesterol screening may also enhance compliance rates. Such technologies yield results that clinicians can present within minutes—obviating a need for post-visit outreach by PCPs or their schedulers. At least two point-of-care systems for cholesterol testing are already available commercially in the U.S.. They require no more than a single drop of a patient's blood to produce results—enabling lancet-based testing to supplant venipuncture-based testing for cholesterol screens. Both point-of-care systems can yield insurance-reimbursable results at break-even or even slightly-profitable levels. One of the systems can even result only total and HDL cholesterol levels—simplifying the task of interpreting lipid profiles.

An evidence-based response to the problem of pediatric cholesterol screening occurring as an isolated blood test demands both historical and modern insights. Citing a 2007 systematic evidence review by the USPSTF that "the optimal age and frequency of testing" children universally for hypercholesterolemia had not yet been established, the NHLBI's 2011 report proposed completing universal screening of children for hypercholesterolemia by specifically 9-11 years old as "a stable time for lipid assessment in children" before most children enter puberty (within which, total cholesterol and LDL-C levels were known to dip). Further justification for highlighting cholesterol screening at 9-11 years old was uncredited in the guideline [42, 70]. However, both Stary's evidence of advanced coronary atherosclerosis arising just beyond the 9-11 age window and accumulating evidence of statin safety and effectiveness among patients at least 10 years old likely influenced the NHLBI's choice [5, 70]. Nevertheless, despite an originally "grade D" evidence rating for the 9-11 years old universal screening window, that window was endorsed as official policy by the AAP while still in pre-print, integrated into the AAP's Bright Futures program's "periodicity schedule" in 2014, and echoed by guidelines from the National Lipid Association in 2015, American Association of Clinical Endocrinologists and American College of Endocrinology in 2017, and the latest "multi-society" guidelines on blood cholesterol management in 2018 [19, 27, 29, 30, 70, 82].

However, not long after the USPSTF closed its 2007 systematic evidence review, Starr and colleagues demonstrated substantially greater discriminatory ability—between individuals genetically-positive versus genetically-negative for FH—from blood LDL-C measurements when the subjects tested were, for instance, <15 versus 45-54 years old [83]. Wald and colleagues contemporarily refined that concept in a meta-analysis. They generated receiver operating characteristic curves of FH detection rates plotted against false-positive rates for total cholesterol and LDL-C as measured from subjects of various age brackets. Whether relying upon total cholesterol or LDL-C, they showed the greatest discriminatory capability between subjects with versus without FH when the subjects being blood tested were 1-9 years old versus any other age group tested (newborns, 10-19-year-olds, and 3 adult cohorts). That finding held regardless of sex, defining FH clinically or genetically, or whether subjects were recruited from lipid clinics or mass screenings. Wald's group also noted, "Within the 1-9 year age group, the screening performance seemed to peak at between 1 and 2 years of age" [84]. From that discovery arose the screening technique for FH index-case-finding today known as "child-parent screening," in which 1-2-year-olds are screened universally for FH, and the relatives of toddlers diagnosed with FH are next offered testing [84–87]. Importantly, Wald and colleagues have demonstrated empirically, in a large trial, that child-parent screening efficiently identifies FH cases [86].

Notions of testing children's blood cholesterol levels in early toddlerhood may be unfamiliar to many PCPs, as no major U.S. guideline has ever endorsed testing cholesterol levels among patients so young. However, there has long been evidence that children's blood cholesterol levels stabilize by the end of infancy—albeit no younger [88–90]. Wald and Martin have summarized several compelling arguments for screening toddlers for hypercholesterolemia. Among their reasons, such timing of pediatric cholesterol screening would: facilitate the premorbid detection of children with homozygous FH, aid the early initiation of "heart healthy" diets for patients with a genetic predisposition for hypercholesterolemia, and facilitate detecting parents with FH before they have incurred or succumbed to MACE [91, 92]. Moreover, screening for lead exposure and anemia already occurs in the U.S. at 1 and 2 years

old, the window recommended by Wald and colleagues for pediatric cholesterol screening [63, 84]. Universal screening for anemia at approximately one year of age is supported by the AAP's Committee on Nutrition [93]. Blood lead level assessment is Federally mandated in the U.S. for all Medicaid-insured 1- and 2-year-olds outside Arizona (where targeted lead screening is permitted), with roughly 40% of U.S. children currently enrolled with Medicaid [94, 95]. Piggybacking of cholesterol screening onto anemia or lead screening manifestly may enhance pediatric cholesterol screening rates and even bolster anemia or lead screening rates by compounding justification for a routine blood draw in toddlerhood.

Last, but not least, although further refinement of cholesterol cutpoints warranting investigation may likely be useful if U.S. guidelines evolve toward targeting pediatric cholesterol screening to toddlerhood, Zawacki and colleagues helpfully have suggested more stringent non-HDL-C cutpoints for determining which 9-11 years old patients warrant further evaluation for hypercholesterolemia. Notably, applying the higher cutpoints recommended by Zawacki and colleagues—which could eventually secure guideline endorsement—would still flag 99% of standard-risk children and 95% of children otherwise at an elevated ASCVD risk who warrant antihyperlipidemic pharmacotherapy while enhancing specificity in the standard-risk group to 96% [71]. The test specificity among children in the group otherwise-at-risk for ASCVD would also improve, to 55%. Though the latter specificity improvement is less robust, that subset of children has other traditional ASCVD risk factors and arguably has greater cause to see a preventive subspecialist irrespective of the child's cholesterol level [96••]. It is reasonable to anticipate that screening performance like that should engender more enthusiasm than current standards from PCPs reluctant to over-refer their patients to subspecialists.

Systems-Based Barriers and Solutions

One systems-based barrier to pediatric lipid screening has been the local inaccessibility of pediatric lipidologists. For instance, roughly one-third of pediatricians confess a lack of comfort in providing appropriate dietary counseling to manage hypercholesterolemia, >95% express doubt about their abilities to motivate patient compliance with appropriate lifestyle changes, and nearly 90% admit discomfort with prescribing statins to children [33]. Such findings should motivate lipidologists to engage further with our trainees at all levels—and with our legislators in support of telehealth offerings. Telemedicine cholesterol care can yield outcomes non-inferior to in-clinic care [97].

Inconsistent health insurance coverage for pediatric cholesterol screening has understandably impeded some screening [32, 39, 66]. Happily, under the Affordable Care Act, all Healthcare Marketplace health insurance plans are mandated to absorb fully the cost of preventive healthcare services recommended under the AAP's Bright Futures program [98, 99]. Furthermore, Tricare Basic, Select, and Prime health plans for U.S. military families fully cover the cost of one lipid profile for children 9-11 years old [100]. Vitally, all Medicaid and CHIP programs at least cover "*for cause*" lipid panel testing throughout childhood. However, even in 2023, universal childhood cholesterol screening is still not universally reimbursable. Minors in the District of Columbia and only 42 states who are insured through Medicaid or CHIP are guaranteed no-cost Early and Periodic Screening, Diagnosis, and Treatment care coverage, including universal cholesterol screening by middle childhood. However, with Medicaid being administered at the state level, children covered under its plans in Alabama, Delaware, Massachusetts, Minnesota, Missouri, Rhode Island, Utah, and Wisconsin lack policy coverage for universal cholesterol screening [98, 99, 101–103]. Lobbying of policymakers in those states is a clear and present need.

Conclusions

The USPSTF is now completing its second systematic review of evidence regarding what value may reside in routine pediatric cholesterol screening since the 2011 release of the NHLBI's guideline on the same subject. Its recently-released draft statement indicates that incongruity between USPSTF and NHLBI guidance will sow misunderstanding and missed screening opportunities [25, 26]. Meanwhile, outside of cholesterol screening's inclusion in the Bright Futures program's periodicity schedule, the AAP has not commented on pediatric cholesterol screenings since 2012 [82]. With the AAP being the US's most authoritative professional body on pediatric healthcare, we encourage the Academy to recruit knowledgeable lipidologists to produce the next generation of pediatric cholesterol screening guidelines. Universal cholesterol screening of children is vital. However, given the poor acceptance of past recommendations in that vein, we urge that those called to the task would not merely recapitulate what has not worked. Instead, they should seek out avenues for garnering the enthusiastic support of *all* PCPs. We do not possess all the light regarding the ideal way to screen children for hypercholesterolemia, but we hope these remarks will at least point in productive directions. Our responsibility to children with hypercholesterolemia is too great for us to shirk from seeking solutions in all corners. We would do well to adopt the attitude exemplified when U.S. Marines officer Oliver Smith famously told a *Time* magazine reporter during the Korean War's losing Chosin Reservoir Campaign: "Retreat, hell! We're

not retreating, we're just advancing in a different direction" [104]!

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References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Centers for Disease Control and Prevention NCfHS. National Vital Statistics System, Mortality 1999-2020 on CDC WONDER Online Database. 2021. http://wonder.cdc.gov/ucd-icd10.html. Accessed 15 Oct 2022.
2. Quality AfHRa. Healthcare Cost and Utilization Project (HCUPnet). 2019. https://datatools.ahrq.gov/hcupnet. Accessed 15 Oct 2022.
3. Kannel WB, Dawber TR, Kagan A, Revotskie N, Stokes J 3rd. Factors of risk in the development of coronary heart disease--six year follow-up experience: The Framingham Study. Ann Intern Med. 1961; https://doi.org/10.7326/0003-4819-55-1-33.
4. Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J. 2017; https://doi.org/10.1093/eurheartj/ehx144.
5. Stary HC. Evolution and progression of atherosclerotic lesions in coronary arteries of children and young adults. Arteriosclerosis. 1989;9(Supplement I):I19-32.
6. Nazif TM, Kalra S, Ali ZA, et al. Percutaneous coronary intervention with bioresorbable scaffolds in a young child. JAMA Cardiol. 2017; https://doi.org/10.1001/jamacardio.2016.4954.
7. Loh WJ, Watts GF. The inherited hypercholesterolemias. Endocrinol Metab Clin North Am. 2022; https://doi.org/10.1016/j.ecl.2022.02.006.
8. de Ferranti SD, Rodday AM, Mendelson MM, Wong JB, Leslie LK. Sheldrick RC: Prevalence of familial hypercholesterolemia in the 1999 to 2012 United States National Health and Nutrition Examination Surveys (NHANES). Circulation. 2016 https://doi.org/10.1161/CIRCULATIONAHA.115.018791.
9. Hopkins PN. Putting into perspective the hazards of untreated familial hypercholesterolemia. J Am Heart Assoc. 2017; https://doi.org/10.1161/JAHA.117.006553.
10. Mundal LJ, Igland J, Veierod MB, et al. Impact of age on excess risk of coronary heart disease in patients with familial hypercholesterolaemia. Heart. 2018; https://doi.org/10.1136/heartjnl-2017-312706.
11. Perak AM, Ning H, de Ferranti SD, Gooding HC, Wilkins JT, Lloyd-Jones DM. Long-term risk of atherosclerotic cardiovascular disease in US adults with the familial hypercholesterolemia phenotype. Circulation. 2016; https://doi.org/10.1161/CIRCULATIONAHA.116.022335.
12. Group SSCobotSBR: Mortality in treated heterozygous familial hypercholesterolaemia: implications for clinical management. Atherosclerosis. 1999; https://doi.org/10.1016/S0021-9150(98)00200-7.
13. Marks D, Thorogood M, Neil HA, Humphries SE. A review on the diagnosis, natural history, and treatment of familial hypercholesterolaemia. Atherosclerosis. 2003; https://doi.org/10.1016/S0021-9150(02)00330-1.
14. Marco-Benedi V, Bea AM, Cenarro A, Jarauta E, Laclaustra M, Civeira F. Current causes of death in familial hypercholesterolemia. Lipids Health Dis. 2022; https://doi.org/10.1186/s12944-022-01671-5.
15. Mundal L, Igland J, Ose L, et al. Cardiovascular disease mortality in patients with genetically verified familial hypercholesterolemia in Norway during 1992-2013. Eur J Prev Cardiol. 2017; https://doi.org/10.1177/2047487316676135.
16. Mabuchi H. Half a century tales of familial hypercholesterolemia (FH) in Japan. J Atheroscler Thromb. 2017; https://doi.org/10.5551/jat.RV16008.
17. Kusters DM, Wiegman A, Kastelein JJ, Hutten BA. Carotid intima-media thickness in children with familial hypercholesterolemia. Circ Res. 2014; https://doi.org/10.1161/CIRCRESAHA.114.301430.
18. Luirink IK, Wiegman A, Kusters DM, et al. 20-year follow-up of statins in children with familial hypercholesterolemia. N Engl J Med. 2019; https://doi.org/10.1056/NEJMoa1816454.
19. Grundy SM, Stone NJ, Bailey AL, et al. AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2018;2019 https://doi.org/10.1161/CIR.0000000000000625.
20. de Ferranti SD, Steinberger J, Ameduri R, et al. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association. Circulation. 2019; https://doi.org/10.1161/CIR.0000000000000618.
21. •• Wilemon KA, Ahmed CD, MP MG, DE MD, Knowles JW, Myers KD. Diagnosis of familial hypercholesterolemia: a work in progress. In: The Present and Future of Cardiometabolic Health: Advances and Expert Perspectives: 19-22 October 2022. Boston, MA; 2022. **This abstract provides the first evidence-based estimate of the proportion of Familial Hypercholesterolemia cases in the United States that already have been identified in clinical practice**.
22. Kastelein JJP, Reeskamp LF, Hovingh GK. Familial hypercholesterolemia: the most common monogenic disorder in humans. J Am Coll Cardiol. 2020; https://doi.org/10.1016/j.jacc.2020.03.058.
23. Finberg L, Bell EF, Dweck HS, et al. Indications for cholesterol testing in children. Pediatrics. 1989; https://doi.org/10.1542/peds.83.1.141.
24. Lauer RM, Barness LA, Clark R, et al. Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. U.S. Department of Health and Human Services, Public Health

Service, National Institutes of Health, National Heart, Lung, and Blood Institute; 1991.
25. Daniels SR, Benuck I, Christakis DA, et al. Summary report. Pediatrics. 2011; https://doi.org/10.1542/peds.2009-2107C.
26. Guirguis-Blake JM, Evans CV, Coppola EL, Redmond N, Perdue LA. Screening for Lipid Disorders in Children and Adolescents: An Evidence Update for the U.S. Preventive Services Task Force. 2023. https://www.uspreventiveservicestaskforce.org/uspstf/document/draft-evidence-review/lipid-disorders-children-adolescents-screening. Accessed 22 June 2023.
27. Jellinger PS, Handelsman Y, Rosenblit PD, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease. Endocr Pract. 2017; https://doi.org/10.4158/EP171764.APPGL.
28. Screening for lipid disorders in children and adolescents: recommendation statement. Am Fam Physician. 2016;94(12):1004A-E.
29. Jacobson TA, Maki KC, Orringer CE, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: part 2. J Clin Lipidol. 2015; https://doi.org/10.1016/j.jacl.2015.09.002.
30. Geoffrey RS, Cynthia B, Graham AB 3rd, et al. recommendations for pediatric preventive health care. Pediatrics. 2014;2014 https://doi.org/10.1542/peds.2013-4096.
31. Allen-Tice C, Steinberger J, Murdy K, Zierhut H. Pediatric cholesterol screening practices in 9- to 11-year-olds in a large midwestern primary care setting. J Clin Lipidol. 2020; https://doi.org/10.1016/j.jacl.2020.01.013.
32. Stipelman C, Young PC, Hemond J, Brown LL, Mihalopoulos NL. Dyslipidemia screening of 9- to 11-year-olds at well-child visits by Utah pediatricians. Clinical Pediatrics. 2017; https://doi.org/10.1177/0009922816684601.
33. de Ferranti SD, Rodday AM, Parsons SK, et al. Cholesterol screening and treatment practices and preferences: a survey of United States pediatricians. J Pediatr. 2017; https://doi.org/10.1016/j.jpeds.2016.12.078.
34. Schefft M, Schroeder AR, Liu D, Nicklas D, Moher J, Quinonez R. Right care for children: top five do's and don'ts. Am Fam Physician. 2019;99(6):376–82.
35. Berger JH, Chen F, Faerber JA, O'Byrne ML, Brothers JA. Adherence with lipid screening guidelines in standard- and high-risk children and adolescents. Am Heart J. 2021; https://doi.org/10.1016/j.ahj.2020.10.058.
36. Gregory EF, Miller JM, Wasserman RC, et al. Adherence to pediatric universal cholesterol testing guidelines across body mass index categories: a CER^2 cohort study. Circ Cardiovasc Qual Outcomes. 2020; https://doi.org/10.1161/CIRCOUTCOMES.119.006519.
37. Berger JH, Faerber JA, Chen F, Lin KY, Brothers JA, O'Byrne ML. Adherence with lipid screening guidelines in children with acquired and congenital heart disease: an observational study using data from the MarketScan commercial and Medicaid databases. J Am Heart Assoc. 2022; https://doi.org/10.1161/JAHA.121.024197.
38. Herrington L, Susi A, Gorman G, Nylund CM, Hisle-Gorman E. Factors affecting pediatric dyslipidemia screening and treatment. Clinical Pediatrics. 2019; https://doi.org/10.1177/0009922819832068.
39. Zhang X, DeSantes K, Dodge A, et al. Practices and attitudes regarding pediatric cholesterol screening recommendations differ between pediatricians and family medicine clinicians. Pediatr Cardiol. 2022; https://doi.org/10.1007/s00246-021-02767-y.
40. Garcia RE, Moodie DS. Routine cholesterol surveillance in childhood. Pediatrics. 1989;84(5):751–5.
41. Ritchie SK, Murphy EC, Ice C, et al. Universal versus targeted blood cholesterol screening among youth: the CARDIAC project. Pediatrics. 2010; https://doi.org/10.1542/peds.2009-2546.
42. Haney EM, Huffman LH, Bougatsos C, Freeman M, Steiner RD, Nelson HD. Screening and treatment for lipid disorders in children and adolescents: systematic evidence review for the US Preventive Services Task Force. Pediatrics. 2007; https://doi.org/10.1542/peds.2006-1801.
43. Zhang Y, An J, Reynolds K, Safford MM, Muntner P, Moran AE. Trends of elevated low-density lipoprotein cholesterol, awareness, and screening among young adults in the US, 2003-2020. JAMA Cardiol. 2022; https://doi.org/10.1001/jamacardio.2022.2641.
44. Ajufo E, deGoma EM, Raper A, Yu KD, Cuchel M, Rader DJ. A randomized controlled trial of genetic testing and cascade screening in familial hypercholesterolemia. Genet Med. 2021; https://doi.org/10.1038/s41436-021-01192-z.
45. Lee C, Rivera-Valerio M, Bangash H, Prokop L, Kullo IJ. New case detection by cascade testing in familial hypercholesterolemia: a systematic review of the literature. Circ Genom Precis Med. 2019; https://doi.org/10.1161/CIRCGEN.119.002723.
46. Kruger V, Redlinger-Grosse K, Walters ST, et al. Development of a motivational interviewing genetic counseling intervention to increase cascade cholesterol screening in families of children with familial hypercholesterolemia. J Genet Couns. 2019; https://doi.org/10.1002/jgc4.1145.
47. Wurtmann E, Steinberger J, Veach PM, Khan M, Zierhut H. Risk communication in families of children with familial hypercholesterolemia: identifying motivators and barriers to cascade screening to improve diagnosis at a single medical center. J Genet Couns. 2018; https://doi.org/10.1007/s10897-018-0290-0.
48. McGowan MP, Cuchel M, Ahmed CD, et al. A proof-of-concept study of cascade screening for familial hypercholesterolemia in the US, adapted from the Dutch model. Am J Prev Cardiol. 2021; https://doi.org/10.1016/j.ajpc.2021.100170.
49. Neuner J, Dimmock D, Kirschner AP, Beaudry H, Paradowski J, Orlando L. Results and lessons of a pilot study of cascade screening for familial hypercholesterolemia in US primary care practices. J Gen Intern Med. 2020; https://doi.org/10.1007/s11606-019-05485-7.
50. Morris JK, Wald DS, Wald NJ. The evaluation of cascade testing for familial hypercholesterolemia. Am J Med Genet A. 2012; https://doi.org/10.1002/ajmg.a.34368.
51. Chen CX, Hay JW. Cost-effectiveness analysis of alternative screening and treatment strategies for heterozygous familial hypercholesterolemia in the United States. Int J Cardiol. 2015; https://doi.org/10.1016/j.ijcard.2014.12.070.
52. Smith AJ, Turner EL, Kinra S, Bodurtha JN, Chien AT. A cost analysis of universal versus targeted cholesterol screening in pediatrics. J Pediatr. 2018; https://doi.org/10.1016/j.jpeds.2018.01.027.
53. Peterson AL, Zhang X, Dodge A, et al. Differences in pediatric cholesterol screening rates between family physicians and pediatricians correlate with conflicting guidelines. Prev Med. 2021; https://doi.org/10.1016/j.ypmed.2021.106732.
54. Physicians AAOF. Clinical preventive service recommendation: lipid disorders. https://www.aafp.org/family-physician/patient-care/clinical-recommendations/all-clinical-recommendations/lipid-disorders.html. Accessed 25 Oct 2022.
55. Walker M. No universal lipid screening for children, says USPSTF: lack of evidence supporting the benefits of dyslipidemia screening. 2016. https://www.medpagetoday.com/endocrinology/metabolicsyndrome/59634. Accessed 26 Oct 2022.
56. Rajendran A, Belanger M, Stone N, Blumenthal RS. Lost opportunities for prevention if clinicians adopt USPSTF statin recommendations. 2022. https://www.healio.com/news/cardiology/20221018/lost-opportunities-for-prevention-if-clini

cians-adopt-uspstf-statin-recommendations. Accessed 30 Oct 2022.
57. Daniels SR. On the US Preventive Services Task Force statement on Screening for Lipid Disorders in Children and Adolescents: one step forward and 2 steps sideways. JAMA Pediatr. 2016; https://doi.org/10.1001/jamapediatrics.2016.2315.
58. de Ferranti SD, Sheldrick RC. USPSTF is unable to recommend for or against lipid screening to identify multifactorial dyslipidaemia in childhood: no recommendation is not without consequences. Evid Based Med. 2017; https://doi.org/10.1136/ebmed-2016-110585.
59. Gidding SS. Why cholesterol testing in children and adolescents matters. JAMA Cardiol. 2016; https://doi.org/10.1001/jamacardio.2016.2871.
60. Urbina EM, de Ferranti SD. Lipid screening in children and adolescents. JAMA. 2016; https://doi.org/10.1001/jama.2016.9671.
61. Wilson DP. Improving Cholesterol Screening in Children-Is Educating Primary Care Providers Enough? J Pediatr. 2022; https://doi.org/10.1016/j.jpeds.2022.06.006.
62. Wilson JMG, Jungner G. Principles and practice of screening for disease, vol. 34. Geneva: World Health Organization; 1968. https://apps.who.int/iris/handle/10665/37650
63. Recommendations for preventive pediatric health care. 2023. https://www.aap.org/periodicityschedule. Accessed 23 Jun 2023.
64. Tanner JL, Stein MT, Olson LM, Frintner MP, Radecki L. Reflections on well-child care practice: a national study of pediatric clinicians. Pediatrics. 2009; https://doi.org/10.1542/peds.2008-2351.
65. Turner K. Well-Child Visits for Infants and Young Children. Am Fam Physician. 2018;98(6):347–53.
66.•• Soukup J, Zierhut HA, Ison HE, 2020 UGCPCo. Universal cholesterol screening among pediatric primary care providers within California and Minnesota: a qualitative assessment of barriers and facilitators. J Pediatr. 2021; https://doi.org/10.1016/j.jpeds.2021.02.065. **This study affords unique depth of insight into the real-world factors that positively and negatively influence the likelihood of children undergoing cholesterol screening in primary care settings in two different states and helps inform effective structural responses to bolster screening rates**
67. Stipelman CH, Stoddard GJ, Smith ER, et al. Quality improvement intervention for universal lipid screening in children aged 9 to 11 years. Clinical Pediatrics. 2019; https://doi.org/10.1177/0009922819884403.
68. McLenon J, Rogers MAM. The fear of needles: a systematic review and meta-analysis. J Adv Nurs. 2019; https://doi.org/10.1111/jan.13818.
69. Orenius T, Säilä H, Mikola K, Ristolainen L. Fear of injections and needle phobia among children and adolescents: an overview of psychological, behavioral, and contextual factors. SAGE Open Nurs. 2018; https://doi.org/10.1177/2377960818759442.
70. Daniels SR, Benuck I, Christakis DA, et al. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. Full Report: U.S. Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute; 2012. https://www.nhlbi.nih.gov/sites/default/files/media/docs/peds_guidelines_full.pdf. Accessed 22 June 2023.
71. Zawacki A, Dodge A, Eickhoff J, et al. Novel lipid thresholds for screening predict the need for pharmacotherapy. J Pediatr. 2018; https://doi.org/10.1016/j.jpeds.2018.07.008.
72. Steiner MJ, Skinner AC, Perrin EM. Fasting might not be necessary before lipid screening: a nationally representative cross-sectional study. Pediatrics. 2011; https://doi.org/10.1542/peds.2011-0844.
73. Szternel L, Krintus M, Bergmann K, Derezinski T, Sypniewska G. Non-fasting lipid profile determination in presumably healthy children: Impact on the assessment of lipid abnormalities. PLoS One. 2018; https://doi.org/10.1371/journal.pone.0198433.
74. Pasic MD, Colantonio DA, Chan MK, Venner AA, Brinc D, Adeli K. Influence of fasting and sample collection time on 38 biochemical markers in healthy children: a CALIPER substudy. Clin Biochem. 2012; https://doi.org/10.1016/j.clinbiochem.2012.07.089.
75. Kubo T, Takahashi K, Furujo M, et al. Usefulness of non-fasting lipid parameters in children. J Pediatr Endocrinol Metab. 2017; https://doi.org/10.1515/jpem-2016-0271.
76. Kolovou GD, Bilianou H, Mikhailidis DP. Postprandial lipemia in children and adolescents. Curr Vasc Pharmacol. 2011; https://doi.org/10.2174/157016111795495521.
77. Patni N, Li X, Adams-Huet B, Garg A. The prevalence and etiology of extreme hypertriglyceridemia in children: data from a tertiary children's hospital. J Clin Lipidol. 2018; https://doi.org/10.1016/j.jacl.2018.01.003.
78. Cresanta JL, Srinivasan SR, Webber LS, Berenson GS. Serum lipid and lipoprotein cholesterol grids for cardiovascular risk screening of children. Am J Dis Child. 1984; https://doi.org/10.1001/archpedi.1984.02140420045016.
79. LaRosa JC, Chambless LE, Criqui MH, et al. Patterns of dyslipoproteinemia in selected North American populations. The Lipid Research Clinics Program Prevalence Study. Circulation. 1986;73(Supplement I):I12–29.
80. Xu J, Du X, Zhang S, Xiang Q, Zhu L, Liu L. The accuracy of four formulas for LDL-C calculation at the fasting and postprandial states. Front Cardiovasc Med. 2022; https://doi.org/10.3389/fcvm.2022.944003.
81. Sajja A, Park J, Sathiyakumar V, et al. Comparison of methods to estimate low-density lipoprotein cholesterol in patients with high triglyceride levels. JAMA Netw Open. 2021; https://doi.org/10.1001/jamanetworkopen.2021.28817.
82. Expert Panel on Integrated Pediatric Guideline for Cardiovascular Health and Risk Reduction. Pediatrics. 2012; https://doi.org/10.1542/peds.2012-0210.
83. Starr B, Hadfield SG, Hutten BA, et al. Development of sensitive and specific age- and gender-specific low-density lipoprotein cholesterol cutoffs for diagnosis of first-degree relatives with familial hypercholesterolaemia in cascade testing. Clin Chem Lab Med. 2008; https://doi.org/10.1515/CCLM.2008.135.
84. Wald DS, Bestwick JP, Wald NJ. Child-parent screening for familial hypercholesterolaemia: screening strategy based on a meta-analysis. BMJ. 2007; https://doi.org/10.1136/bmj.39300.616076.55.
85. Wald DS, Bestwick JP. Reaching detection targets in familial hypercholesterolaemia: comparison of identification strategies. Atherosclerosis. 2020; https://doi.org/10.1016/j.atherosclerosis.2019.11.028.
86. Wald DS, Bestwick JP, Morris JK, Whyte K, Jenkins L, Wald NJ. Child-parent familial hypercholesterolemia screening in primary care. N Engl J Med. 2016; https://doi.org/10.1056/NEJMoa1602777.
87. Wald DS, Wald NJ. Integration of child-parent screening and cascade testing for familial hypercholesterolaemia. J Med Screen. 2019; https://doi.org/10.1177/0969141318796856.
88. Sporik R, Johnstone JH, Cogswell JJ. Longitudinal study of cholesterol values in 68 children from birth to 11 years of age. Arch Dis Child. 1991; https://doi.org/10.1136/adc.66.1.134.
89. Kallio MJ, Salmenpera L, Siimes MA, Perheentupa J, Miettinen TA. Tracking of serum cholesterol and lipoprotein levels from the first year of life. Pediatrics. 1993; https://doi.org/10.1542/peds.91.5.949.
90. Rask-Nissilä L, Jokinen E, Viikari J, et al. Impact of dietary intervention, sex, and apolipoprotein E phenotype on tracking of serum lipids and apolipoproteins in 1- to 5-year-old children: the Special Turku Coronary Risk Factor Intervention Project

(STRIP). Arterioscler Thromb Vasc Biol. 2002; https://doi.org/10.1161/hq0302.104516.
91. Wald DS, Martin AC. Further response to 'Decision to reject screening for familial hypercholesterolaemia is flawed' by Wald and Martin. Arch Dis Child. 2022; https://doi.org/10.1136/archdischild-2021-322934.
92. Pahkala K, Laitinen TT, Niinikoski H, et al. Effects of 20-year infancy-onset dietary counselling on cardiometabolic risk factors in the Special Turku Coronary Risk Factor Intervention Project (STRIP): 6-year post-intervention follow-up. Lancet Child Adolesc Health. 2020;4(5):359–69.
93. Baker RD, Greer FR. Nutrition TCo: Diagnosis and prevention of iron deficiency and iron-deficiency anemia in infants and young children (0-3 years of age). Pediatrics. 2010; https://doi.org/10.1542/peds.2010-2576.
94. Mykyta L, Keisler-Starkey K, Bunch L. More children were covered by Medicaid and CHIP in 2021. 2022. https://www.census.gov/library/stories/2022/09/uninsured-rate-of-children-declines.html. Accessed 30 Oct 2022.
95. Lead screening. https://www.medicaid.gov/medicaid/benefits/early-and-periodic-screening-diagnostic-and-treatment/lead-screening/index.html. Accessed 7 Nov 2022.
96.•• Gidding SS, Colangelo LA, Nwabuo CC, et al. PDAY risk score predicts cardiovascular events in young adults: the CARDIA study. Eur Heart J. 2022; https://doi.org/10.1093/eurheartj/ehac009. **This study validates, for the first time, good prediction of incident atherosclerotic cardiovascular disease in middle age based upon a metric—the Pathobiological Determinants of Atherosclerosis in Youth score—calculated in very young adulthood (and calculable even in adolescence) from analysis of such parameters as Non-High-Density-Lipoprotein-Cholesterol, Body Mass Index, Blood Pressure, and Hemoglobin A1c level**
97. Mabeza RMS, Maynard K, Tarn DM. Influence of synchronous primary care telemedicine versus in-person visits on diabetes, hypertension, and hyperlipidemia outcomes: a systematic review. BMC Prim Care. 2022; https://doi.org/10.1186/s12875-022-01662-6.
98. Preventive care benefits for children. https://www.healthcare.gov/preventive-care-children. Accessed 30 Oct 2022.
99. Bright futures. https://mchb.hrsa.gov/programs-impact/bright-futures. Accessed 30 Oct 2022.
100. Tricare policy manual 6010.60-M. 2015. https://manuals.health.mil/pages/DisplayManualHtmlFile/2022-10-20/AsOf/TP15/D:/Files/Temp/TP15/C-103/xml/AsOf/c7s2_2.html. Accessed 30 Oct 2022.
101. Children's health care coverage fact sheets. https://www.aap.org/en/advocacy/childrens-health-care-coverage-fact-sheets. Accessed 31 Oct 2022.
102. The code of Federal regulations. https://www.ecfr.gov/current/title-42/chapter-IV/subchapter-C/part-441/subpart-B. Accessed 31 Oct 2022.
103. Compilation of the Social Security laws. https://www.ssa.gov/OP_Home/ssact/title19/1905.htm. Accessed 31 Oct 2022.
104. War: retreat of the 20,000. https://content.time.com/time/subscriber/article/0,33009,858986,00.html. Accessed 31 Oct 2022.