The US Preventive Services Task Force Recommendation on Screening for Asymptomatic Celiac Disease
A Dearth of Evidence

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In this issue of *JAMA*, the US Preventive Services Task Force (USPSTF) critically examines screening for celiac disease in asymptomatic adults, adolescents, and children. Celiac disease, one of the most common lifelong disorders in the United States, exhibits a broad spectrum of clinical presentations from subtle or no symptoms to severe malabsorption. The rate of diagnosis of celiac disease has substantially increased over the past 30 years, in part explained by increased awareness but perhaps also by a true increase in the disease. The current prevalence of celiac disease is estimated at 0.71% among US adults and 0.76% among US children. However, most celiac disease in the population remains undetected, despite wide availability of accurate serologic tests for the disease. Screening could be one option to detect this condition, especially among populations at high risk of celiac disease but who have not yet developed symptoms. The USPSTF, having set an appropriately high bar, concludes that “the current evidence is insufficient to assess the balance of benefits and harms of screening for celiac disease in asymptomatic persons” and has recommended that more research is needed in this area.

Although the USPSTF review of this topic may be criticized as premature, the USPSTF has appropriately identified the need for data to provide direction in this fundamental area. The USPSTF applied rigorous methodology to address the effectiveness of screening for celiac disease in an asymptomatic population and found the evidence insufficient. The conclusion and recommendation of the task force will undoubtedly be disappointing for many clinicians as well as some patients. By design, the task force focuses solely on asymptomatic persons or persons with unrecognized symptoms; screening the general population could potentially detect not only asymptomatic patients but also patients who lack typical symptoms such as weight loss, diarrhea, or malabsorption.

Celiac disease is now recognized as a heterogeneous disease that largely presents with atypical symptoms, symptoms far removed from the gastrointestinal tract, or no symptoms at all. Even though these patients are not asymptomatic, they usually lack sufficient clinical features, such as chronic diarrhea and weight loss, that would enable diagnosis. The opportunity to help these patients with undetected celiac disease could be missed without effective case-finding strategies that could include screening. The symptoms of celiac disease can be so insidious that patients may not even realize they have symptoms and not even acknowledge them. In general-population screening studies (and indeed in birth cohort studies), most patients with celiac disease lack any excess of symptoms compared with persons without celiac disease.

Data from the recent National Health and Nutrition Examination Survey suggest that current practice for the detection of celiac disease, which mainly relies on the development of sufficient typical symptoms along with clinical suspicion, is ineffective, missing approximately 70% of affected individuals. Patients with atypical or nonspecific symptoms often report a delay in diagnosis of celiac disease that may last for years. Thus, screening would enable the earlier detection of symptomatic but undetected celiac disease and shorten the duration of symptoms.

The USPSTF review highlights the lack of the data on natural history of silent or subclinical celiac disease and whether these patients progress to symptomatic celiac disease, develop consequent complications, or have spontaneous regression of this condition. In addition to 3 US studies described in this USPSTF review, a recent large US population-based study reported that the 5-year cumulative incidence rate of subsequent clinical diagnosis was 11% among individuals with positive celiac serology findings on archived samples. Progession to diagnosed celiac disease may not be the only outcome of seropositivity, because spontaneous regression occurs in 20% to 50% of antibody-positive children despite continuing gluten consumption, especially among children with type 1 diabetes mellitus. In a study of 32 children aged 2 to 4 years, 6 (20%) who had positive endomysial antibodies and villous atrophy and who were asymptomatic remained so over 10 years while consuming a gluten-containing diet. It is clear that more research is needed to understand the disease course of persons with silent or subclinical celiac disease, including whether there is an abrupt or slow progression toward symptomatic celiac disease, whether the disease in some individuals will remain clinically silent, and what factors determine the clinical course and outcomes among these individuals (Figure). The more crucial issue is whether any of these individuals have decrements in nutrition and health, and subsequent excess mortality, that could be avoided with earlier detection.

The USPSTF review also addressed the diagnostic accuracy of tests for celiac disease in asymptomatic patients. Overall, the best serologic test for celiac disease is currently tissue
transglutaminase (tTG)-IgA, which has a high sensitivity and specificity for untreated celiac disease, especially in high-risk groups. However, the positive predictive value declines when this test is used in settings with low pretest prevalence, such as in the general population. The diagnostic accuracy is important in these low-prevalence settings that include many asymptomatic individuals, so that the use of invasive tests can be minimized. More nuanced approaches to serologic tests, such as combining the highly sensitive tTG-IgA with endomysial antibodies, very high titer tTG-IgA, or serially positive tTG by radioimmunoassay, have a diagnostic accuracy that rivals that of traditional biopsy-based approaches. The recent European Society for Paediatric Gastroenterology Hepatology and Nutrition guidelines for children have a nearly 100% positive predictive value for celiac disease when anti-tTG is 10 times the upper limit of normal or higher, regardless of symptom status.19,20

Although the USPSTF review only discussed 2 non-US studies on the diagnostic accuracy in asymptomatic persons, studies conducted in the general population may be informative. In a study involving 1000 participants, parallel serologic testing and biopsies were undertaken in a random sampling of the general population, demonstrating very high accuracy (approximately 99%) for sequentially positive tTG-IgA and endomysial serology in predicting histologic changes of celiac disease.10 Furthermore, a US study of 3800 attendees at a preventive health fair also showed high positive predictive values (94% for celiac disease) in an adult general population, even though only 60% of people who were positive for tTG-IgA and subsequent endomysial antibodies underwent endoscopic biopsy.21 Neither study showed a correlation between gastrointestinal symptoms and seropositivity. Overall, for settings in which the accuracy of tTG-IgA as a single test is insufficient, these screening strategies can achieve the positive predictive value sufficient for detection of celiac disease in the general population.

Although no studies have directly addressed the benefits and harms of treatment of screen-detected asymptomatic ce-


