JAMA | US Preventive Services Task Force | RECOMMENDATION STATEMENT

# Screening for Celiac Disease
## US Preventive Services Task Force Recommendation Statement

US Preventive Services Task Force

**IMPORTANCE** Celiac disease is caused by an immune response in persons who are genetically susceptible to dietary gluten, a protein complex found in wheat, rye, and barley. Ingestion of gluten by persons with celiac disease causes immune-mediated inflammatory damage to the small intestine.

**OBJECTIVE** To issue a new US Preventive Services Task Force (USPSTF) recommendation on screening for celiac disease.

**EVIDENCE REVIEW** The USPSTF reviewed the evidence on the accuracy of screening in asymptomatic adults, adolescents, and children; the potential benefits and harms of screening vs not screening and targeted vs universal screening; and the benefits and harms of treatment of screen-detected celiac disease. The USPSTF also reviewed contextual information on the prevalence of celiac disease among patients without obvious symptoms and the natural history of subclinical celiac disease.

**FINDINGS** The USPSTF found inadequate evidence on the accuracy of screening for celiac disease, the potential benefits and harms of screening vs not screening or targeted vs universal screening, and the potential benefits and harms of treatment of screen-detected celiac disease.

**CONCLUSIONS AND RECOMMENDATION** The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for celiac disease in asymptomatic persons. (I statement)

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The US Preventive Services Task Force (USPSTF) makes recommendations about the effectiveness of specific preventive care services for patients without obvious related signs or symptoms.

It bases its recommendations on the evidence of both the benefits and harms of the service and an assessment of the balance. The USPSTF does not consider the costs of providing a service in this assessment.

The USPSTF recognizes that clinical decisions involve more considerations than evidence alone. Clinicians should understand the evidence but individualize decision making to the specific patient or situation. Similarly, the USPSTF notes that policy and coverage decisions involve considerations in addition to the evidence of clinical benefits and harms.

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**Summary Video** Screening for Celiac Disease: US Preventive Services Task Force Recommendation Statement

## Summary of Recommendation and Evidence

The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for celiac disease in asymptomatic persons (I statement) (**Figure 1**). See the Summary Video.

## Rationale

### Importance

Celiac disease is a multisystem autoimmune disorder in genetically predisposed adults and children that is triggered by dietary gluten. Ingestion of gluten by persons with celiac disease causes immune-mediated inflammatory damage to the small intestine, which can cause gastrointestinal and nongastrointestinal illness. The clinical presentation, severity of symptoms, and natural history of the disease varies and includes asymptomatic (or "silent") celiac disease.

In studies of US populations, the estimated prevalence of celiac disease among adults ranges from 0.40% to 0.95%.[1] Prevalence is higher than average among non-Hispanic whites, persons with a family history of celiac disease, and persons with other autoimmune conditions.[2]

### Detection

The USPSTF found inadequate evidence regarding the accuracy of screening tests for celiac disease in asymptomatic populations.

Figure 1. US Preventive Services Task Force Grades and Levels of Certainty

What the USPSTF Grades Mean and Suggestions for Practice

| Grade | Definition | Suggestions for Practice |
|---|---|---|
| A | The USPSTF recommends the service. There is high certainty that the net benefit is substantial. | Offer or provide this service. |
| B | The USPSTF recommends the service. There is high certainty that the net benefit is moderate, or there is moderate certainty that the net benefit is moderate to substantial. | Offer or provide this service. |
| C | The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small. | Offer or provide this service for selected patients depending on individual circumstances. |
| D | The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits. | Discourage the use of this service. |
| I statement | The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined. | Read the Clinical Considerations section of the USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms. |

USPSTF Levels of Certainty Regarding Net Benefit

| Level of Certainty | Description |
|---|---|
| High | The available evidence usually includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies. |
| Moderate | The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as<br>the number, size, or quality of individual studies.<br>inconsistency of findings across individual studies.<br>limited generalizability of findings to routine primary care practice.<br>lack of coherence in the chain of evidence.<br>As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion. |
| Low | The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of<br>the limited number or size of studies.<br>important flaws in study design or methods.<br>inconsistency of findings across individual studies.<br>gaps in the chain of evidence.<br>findings not generalizable to routine primary care practice.<br>lack of information on important health outcomes.<br>More information may allow estimation of effects on health outcomes. |
| The USPSTF defines certainty as "likelihood that the USPSTF assessment of the net benefit of a preventive service is correct." The net benefit is defined as benefit minus harm of the preventive service as implemented in a general, primary care population. The USPSTF assigns a certainty level based on the nature of the overall evidence available to assess the net benefit of a preventive service. | |

## Benefits of Early Detection and Intervention or Treatment

The USPSTF found inadequate evidence on the effectiveness of screening for celiac disease in asymptomatic adults, adolescents, and children with regard to morbidity, mortality, or quality of life. The USPSTF also found inadequate evidence on the effectiveness of targeted screening in persons who are at increased risk for celiac disease (eg, persons with family history or other risk factors).

The USPSTF found inadequate evidence on the effectiveness of treatment of screen-detected, asymptomatic celiac disease to improve morbidity, mortality, or quality of life compared with no treatment or treatment initiated after clinical diagnosis.

## Harms of Early Detection and Intervention or Treatment

The USPSTF found inadequate evidence on the harms of screening for or treatment of celiac disease.

## USPSTF Assessment

The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for celiac disease in asymptomatic persons. Evidence is lacking, and the balance of benefits and harms cannot be determined.

Figure 2. Screening for Celiac Disease: Clinical Summary

| | |
|---|---|
| Population | Asymptomatic adults, adolescents, and children |
| Recommendation | No recommendation.<br>Grade: I (insufficient evidence) |

| | |
|---|---|
| Risk Assessment | Persons at increased risk for celiac disease include those who have a positive family history (eg, a first- or second-degree relative) and persons with other autoimmune diseases (eg, type 1 diabetes mellitus, inflammatory luminal gastrointestinal disorders, Down syndrome, Turner syndrome, IgA deficiency, and IgA nephropathy). |
| Screening Tests | Screening for celiac disease is typically not performed in average-risk persons. The standard method of diagnosing celiac disease is the tissue transglutaminase IgA test, followed by intestinal biopsy for histologic confirmation. |
| Treatment | Treatment of celiac disease is lifelong adherence to a gluten-free diet, which reverses disease manifestations in a majority of patients. |
| Balance of Benefits and Harms | The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for celiac disease in asymptomatic persons. |

For a summary of the evidence systematically reviewed in making this recommendation, the full recommendation statement, and supporting documents, please go to https://www.uspreventiveservicestaskforce.org.

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## Clinical Considerations

### Patient Population Under Consideration

This recommendation applies to adults, adolescents, and children who do not have signs or symptoms of celiac disease (**Figure 2**).

### Suggestions for Practice Regarding the I Statement

#### Potential Preventable Burden

Classic celiac disease is associated with symptoms of malabsorption, including diarrhea, abdominal pain, and weight loss. It may also manifest as nonspecific, nongastrointestinal symptoms, including anemia, osteoporosis, chronic fatigue, peripheral neuropathy or ataxia, and short stature.[3] Data from the United States suggest that some patients may have symptoms for years before being diagnosed.[4] Evidence also suggests that celiac disease is associated with excess mortality, intestinal adenocarcinoma, and lymphoma; however, evidence is insufficient as to whether silent, or asymptomatic, disease has the same risk as symptomatic disease.[2,5-7]

In 3 US-based studies, the prevalence of laboratory-confirmed celiac disease ranged from 0.40% to 0.95% among adults.[1] Some variations in prevalence can be attributed in part to the method used to confirm diagnosis.[2] For example, some population-based studies on prevalence rely on serologic testing without histologic confirmation, which may result in false-positive diagnoses and overestimate prevalence. However, in a systematic review of 38 studies from North America and Western Europe, prevalence of celiac disease was similar among studies that included biopsy confirmation (0.15%-1.90%) and among studies that did not include biopsy confirmation (0.15%-2.70%).[1]

Celiac disease affects children, adolescents, and adults. Seroconversion to antibodies associated with celiac disease may occur at any time, and disease progression can take months or years, if it occurs at all. Data suggest that the average age at diagnosis is now in the fourth to sixth decade of life.[8,9] Data are limited on the proportion of persons with silent celiac disease (positive histology findings but no symptoms) or potential celiac disease (positive serology findings but mild or no intestinal damage on biopsy) who later develop symptomatic celiac disease. Three long-term studies of US adults with follow-up ranging from 10 to 45 years reported rates of progression from positive serology findings to clinical diagnosis of celiac disease of 0% to 15%.[10-12]

Persons at increased risk for celiac disease include those who have a positive family history (eg, a first- or second-degree relative), with an estimated prevalence of 5% to 20%,[13] and persons with other autoimmune diseases (eg, type 1 diabetes mellitus, inflammatory luminal gastrointestinal disorders, Down syndrome, Turner syndrome, IgA deficiency, and IgA nephropathy).[14] Several specialty societies recommend screening in these populations.[15-17] Reported prevalence among racial/ethnic minorities is lower than among non-Hispanic whites.[2,5]

#### Potential Harms

Potential harms of screening for celiac disease in asymptomatic populations include false-positive, inconclusive, or unnecessary serologic test results and biopsies, with possible anxiety or complications from testing. Based on estimated likelihood ratios in the general population,[2] the positive predictive value of serologic testing for celiac disease is 12% to 40%, assuming a prevalence of approximately 1%. In a higher-risk population, the positive predictive value is 40% to 80%, depending on the serologic test used and whether the assumed prevalence is 5% or 10%. Some patients with positive serology findings who do not undergo histologic confirmation may make efforts to avoid dietary gluten, which can increase costs and burdens and may result in limitations on quality of life. Limited evidence from 5 long-term follow-up studies (3 studies of patients with positive serology findings; 2 studies of children with biopsy confirmation) has shown that some persons who are diagnosed with

celiac disease may never develop symptoms or complications; thus, overdiagnosis is also a potential concern.[10-12,18,19]

### Current Practice

Reliable data on the frequency of screening for celiac disease in asymptomatic persons in clinical practice are not available.[20] It is not known how many patients with positive serology findings without biopsy confirmation are treated with a gluten-free diet.

### Screening Tests

Screening for celiac disease is typically not performed in average-risk persons.[2] The standard method of diagnosing celiac disease in symptomatic persons older than 2 years is the tissue transglutaminase (tTG) IgA test, followed by intestinal biopsy for histologic confirmation.[2]

## Treatment and Interventions

Treatment of celiac disease is lifelong adherence to a gluten-free diet, which reverses disease manifestations in a majority of patients.[2]

## Additional Approaches to Prevention

The National Institute of Diabetes and Digestive and Kidney Diseases provides current, comprehensive, science-based information about the symptoms, diagnosis, and treatment of celiac disease.[21]

## Other Considerations

### Research Needs and Gaps

Studies that randomly assign participants to screening vs no screening and evaluate clinical outcomes are lacking. However, screening studies that target populations at increased risk for celiac disease are likely to be more informative than trials that target the general population, because of the higher prevalence of disease, and should be given higher priority. More information is needed about the accuracy of serologic testing in asymptomatic persons, particularly those with disease risk factors.

Treatment studies in screen-detected, asymptomatic persons are also needed to understand the effects of adherence to a gluten-free diet (compared with no dietary intervention), as well as the effects of immediate vs delayed dietary changes (ie, at the time of screen-detected diagnosis vs when symptoms develop). Ideally, studies would report both short-term effects on symptoms and quality of life and long-term outcomes (eg, osteoporotic fractures, cancer, and mortality). As for screening, treatment studies focused on asymptomatic persons at high risk for celiac disease who screen positive would be helpful for developing guidance for this population and may be faster and more efficient to complete than other study designs. More research is needed to better understand the natural history of positive serology in patients without histologic changes or with histologic confirmation but no symptoms. Also, treatment studies should report results stratified according to baseline histologic findings, given current uncertainty about the natural history of celiac disease in persons with mild histologic abnormalities.

## Discussion

### Burden of Disease

Celiac disease is caused by an immune response in persons who are genetically susceptible to dietary gluten, a protein complex found in wheat, rye, and barley. Ingestion of gluten by persons with celiac disease causes immune-mediated inflammatory damage to the small intestine mucosa, resulting in malabsorption of nutrients.

Celiac disease can have several different presentations. Classic celiac disease is associated with diarrhea, abdominal pain, and weight loss. However, celiac disease is also associated with nongastrointestinal, nonspecific manifestations of disease such as anemia, osteoporosis, chronic fatigue, peripheral neuropathy or ataxia, aphthous stomatitis, dermatitis herpetiformis, infertility, recurrent fetal loss, or short stature.[3] Children may also experience pubertal delay and dental enamel defects.[22] For patients with subclinical disease, symptoms may be mild and not recognized until after initiation of a gluten-free diet. Patients with silent, or asymptomatic, celiac disease have been diagnosed by serologic testing and intestinal biopsy but do not have the typical signs or symptoms of celiac disease. Patients with potential celiac disease have positive serology findings and mild or no intestinal damage on biopsy; they may or may not have symptoms. The natural history of silent and potential celiac disease is not well understood, and it is not clear if they represent progressive stages of celiac disease or distinct subtypes.[2]

Data on the prevalence of silent celiac disease in the United States, as well as the proportion of these individuals who later develop symptomatic celiac disease, are limited.[2] Reported prevalence of celiac disease in the literature varies due to the different racial/ethnic populations studied and the method used to confirm diagnosis.[2] In a systematic review of 38 studies from North America and Western Europe, prevalence was similar among studies that included biopsy confirmation (0.15%-1.90%) and among studies that did not (0.15%-2.70%).[1] In the 3 US-based studies, prevalence among adults ranged from 0.40% to 0.95%.[1]

### Scope of Review

The USPSTF reviewed the evidence on the accuracy of screening in asymptomatic adults, adolescents, and children; the potential benefits and harms of screening vs not screening, as well as targeted vs universal screening; and the benefits and harms of treatment of screen-detected celiac disease. For questions regarding the benefits and harms of screening and treatment, outcomes of interest included morbidity, mortality, and quality of life. The USPSTF also reviewed contextual information on the prevalence of celiac disease among patients without evident symptoms and the natural history of subclinical or silent celiac disease.[2] The USPSTF did not review the evidence on nonceliac gluten sensitivity because this condition is defined based on the presence of symptoms rather than diagnostic tests, and it is not thought to lead to the health complications associated with celiac disease.[23]

### Accuracy of Screening Tests

A recent good-quality systematic review on the accuracy of diagnostic tests for celiac disease, which included studies enrolling both persons with symptoms and those whose symptom status was not described, found high strength of evidence that the tTG IgA test has high

(>90%) sensitivity and specificity and endomysial antibody (EMA) IgA tests have high specificity, based on consistent results from prior systematic reviews and new studies.[24] This systematic review included only 2 studies reporting diagnostic accuracy in asymptomatic persons at higher risk for celiac disease, due to other autoimmune disorders or family history, and no studies in asymptomatic persons at average risk. These 2 cross-sectional studies, which were both conducted outside the United States, found lower sensitivity and specificity for the tTG and EMA IgA tests (sensitivity, 57%-71%; specificity, 83%-98%), compared with studies that did not restrict enrollment to asymptomatic patients. One study was conducted in Iraq among patients with type 1 diabetes mellitus, no symptoms of celiac disease, and no family history of celiac disease or thyroid disorders. Sensitivity was 71% for both the tTG and EMA IgA tests and specificity was 93% for the tTG test and 96% for the EMA IgA test.[25] The second study was conducted in the Czech Republic among children and adolescents at higher risk for celiac disease due to family history or a diagnosis of type 1 diabetes mellitus. Among asymptomatic patients, specificity and sensitivity of detecting antitransglutaminase levels of more than 10 times the upper limit of normal and a positive EMA IgA test result in patients with a Marsh histologic classification of stage 2 or 3 were 67% and 83%, respectively. Among first-degree relatives of patients with celiac disease (n = 32), specificity was 70% and sensitivity was 81%. Among patients with type 1 diabetes mellitus (n = 40), specificity was 64% and sensitivity was 93%.[26]

### Effectiveness of Early Detection or Treatment

The USPSTF found no trials or controlled observational studies on the benefits of screening vs not screening or targeted vs universal screening in asymptomatic populations.

The USPSTF found no studies on the benefits of treatment of screen-detected celiac disease compared with treatment initiated after clinical diagnosis. The USPSTF found 1 small fair-quality trial on the benefits of treatment of screen-detected, asymptomatic adults compared with no treatment.[27] This study (n = 40) reported that after 1 year, a gluten-free diet was associated with improvements in histopathologic findings and small improvements in 3 of 5 gastrointestinal symptoms that were statistically but not clinically significant (<1 point on a 7-point scale). While there was also improvement in anxiety, no other measures of health-related quality of life showed improvements, and social functioning was worse in the group being treated with a gluten-free diet. After 2 years, more than 90% of participants in the intervention group reported adherence to the gluten-free diet, but there were no differences between the 2 groups in serology or subjective perception of health as measured by the visual analog scale.

### Potential Harms of Screening or Treatment

The USPSTF found no trials or controlled observational studies on the harms of screening for celiac disease in asymptomatic populations. Potential harms of screening include false-positive, inconclusive, or unnecessary serologic test results and biopsies, with possible anxiety or complications from testing. However, the USPSTF found no studies on these harms. A subset of patients with biopsy-confirmed celiac disease may never develop symptoms; therefore, overdiagnosis is also a potential concern.[2]

One small fair-quality trial of treatment with a gluten-free diet[27] reported no withdrawals due to major symptoms or complications. The USPSTF found no other studies on the harms of treatment with a gluten-free vs nongluten-free diet in persons with screen-detected celiac disease.

### Estimate of Magnitude of Net Benefit

The USPSTF found inadequate evidence on the accuracy of screening for celiac disease in asymptomatic populations. The USPSTF found inadequate evidence on the potential benefits and harms of screening vs not screening, as well as targeted vs universal screening in asymptomatic populations. The USPSTF found inadequate evidence on the potential benefits and harms of treatment of screen-detected celiac disease compared with no treatment or treatment after clinical diagnosis. Therefore, the USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for celiac disease in asymptomatic persons.

### Response to Public Comment

A draft version of this recommendation statement was posted for public comment on the USPSTF website from May 3 to May 30, 2016. Many comments described patients' personal experience of a delayed diagnosis because of atypical or nonspecific symptoms. In response, the USPSTF expanded the "Suggestions for Practice" section to call attention to the prevalence of nonclassical symptoms, including anemia and osteoporosis, and delayed diagnosis. Another frequently raised concern was the higher risk among relatives of patients with celiac disease and patients with other autoimmune diseases. The USPSTF revised the "Research Needs and Gaps" section to emphasize the importance of developing evidence to guide clinical practice for this population.

## Recommendations of Others

The American Academy of Family Physicians has concluded that the current evidence is insufficient to assess the balance of benefits and harms of screening for celiac disease in asymptomatic persons.[28] The American College of Gastroenterology recommends that asymptomatic persons with a first-degree relative who has a confirmed diagnosis of celiac disease be considered for testing. Patients with type 1 diabetes mellitus should be tested for celiac disease if there are any digestive symptoms, signs, or laboratory evidence suggestive of celiac disease.[15]

The National Institute for Health and Care Excellence recommends offering serologic testing to persons with a first-degree relative with celiac disease or persons with type 1 diabetes mellitus or autoimmune thyroid disease on diagnosis. Serologic testing for celiac disease should be considered for persons with any of the following: metabolic bone disorder (reduced bone mineral density or osteomalacia), unexplained neurologic symptoms (particularly peripheral neuropathy or ataxia), unexplained subfertility or recurrent miscarriage, persistently elevated liver enzyme levels with unknown cause, dental enamel defects, Down syndrome, or Turner syndrome.[16]

The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition recommends testing for celiac disease in asymptomatic children who have conditions associated with celiac disease (type 1 diabetes mellitus, autoimmune thyroiditis, Down syndrome, Turner syndrome, Williams syndrome,

or selective IgA deficiency) or a first-degree relative with celiac disease. It recommends testing these children beginning around age 3 years, provided they have had an adequate gluten-containing diet for at least 1 year prior. It also recommends that asymptomatic, at-risk children with negative serology findings be considered for repeat testing.[17]

## ARTICLE INFORMATION

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