JAMA | US Preventive Services Task Force | EVIDENCE REPORT

Screening for Celiac Disease
Evidence Report and Systematic Review for the US Preventive Services Task Force

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IMPORTANCE Silent or subclinical celiac disease may result in potentially avoidable adverse health consequences.

OBJECTIVE To review the evidence on benefits and harms of screening for celiac disease in asymptomatic adults, adolescents, and children 3 years and older for the US Preventive Services Task Force.

DATA SOURCES Ovid MEDLINE, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews, searched to June 14, 2016.

STUDY SELECTION Randomized clinical trials and cohort or case-control studies on clinical benefits and harms of screening vs no screening for celiac disease or treatment vs no treatment for screen-detected celiac disease; studies on diagnostic accuracy of serologic tests for celiac disease.

DATA EXTRACTION AND SYNTHESIS One investigator abstracted data, a second checked data for accuracy, and 2 investigators independently assessed study quality using predefined criteria.

MAIN OUTCOMES AND MEASURES Cancer incidence, gastrointestinal outcomes, psychological outcomes, child growth outcomes, health outcomes resulting from nutritional deficiencies, quality of life, mortality, and harms of screening. No meta-analytic pooling was done.

RESULTS One systematic review and 3 primary studies met inclusion criteria. No trials of screening for celiac disease were identified. One recent, good-quality systematic review of 56 original studies and 12 previous systematic reviews (sample sizes of primary studies ranging from 62 to more than 12 000 participants) found IgA tissue transglutaminase was associated with high accuracy (sensitivity and specificity both >90%) for diagnosing celiac disease. IgA endomysial antibodies tests were associated with high specificity. Only 2 studies of serologic tests for celiac disease involving 62 and 158 patients were conducted in asymptomatic populations and reported lower sensitivity (57% and 71%). One fair-quality, small (n = 40) Finnish treatment trial of asymptomatic adults with screen-detected celiac disease based on positive serologic findings found initiation of a gluten-free diet associated with small improvement in gastrointestinal symptoms compared with no gluten-free diet (difference less than 1 point on a scale of 1 to 7) at 1 year, with no differences on most measures of quality of life. No withdrawals due to adverse events occurred during the trial; no other harms were reported. No studies were identified that addressed the other outcomes.

CONCLUSIONS AND RELEVANCE Although some evidence was found regarding diagnostic accuracy of tests for celiac disease, little or no evidence was identified to inform most of the key questions related to benefits and harms of screening for celiac disease in asymptomatic individuals. More research is needed to understand the effectiveness of screening and treatment for celiac disease, accuracy of screening tests in asymptomatic persons, and optimal screening strategies.

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Celiac disease is a multisystem autoimmune disorder triggered by exposure to dietary gluten in genetically predisposed individuals. A systematic review of 38 studies published from 1992 to 2004 found celiac disease prevalence estimates in North America and Western Europe that ranged from 0.15% to 1.87%, based on studies with intestinal biopsy confirmation of positive serologic test results; estimates in studies of US adults ranged from 0.40% to 0.95%.[1] More recently, a study of 7798 persons 6 years or older who participated in the 2009-2010 National Health and Nutrition Examination Survey found a celiac disease prevalence of 0.71%, based on positive serologic test results or a reported celiac disease diagnosis and being on a gluten-free diet.[2] Celiac disease can be diagnosed at any age and presents more frequently in adults than in children.[3-6] The clinical presentation and natural history of celiac disease vary. Treatment is removal of dietary gluten. Classic celiac disease presents with symptoms of malabsorption and various nongastrointestinal signs and symptoms. Celiac disease may also be silent (the patient meets celiac disease diagnostic criteria but does not manifest common symptoms or signs) or subclinical (symptoms are below the celiac disease testing threshold). For silent or subclinical celiac disease, screening might enable initiation of treatment before overt symptoms develop, alleviate mild but unrecognized symptoms, prevent malabsorption and associated nutritional deficiencies, or prevent other adverse health consequences, such as gastrointestinal malignancy.[7-9] Evidence on the natural history of silent celiac disease is limited, although 3 US studies found that 0% to 15% of patients with positive serologic test results for celiac disease (without histologic confirmation) developed symptoms after 10 to 45 years.[10-12]

The purpose of this report was to systematically review the evidence on benefits and harms of celiac disease screening. The report was commissioned by the US Preventive Services Task Force (USPSTF) to inform a recommendation statement on celiac disease screening in persons 3 years or older. The USPSTF has not previously addressed celiac disease screening.

Methods

Scope of Review

Detailed methods are available in the full evidence report available at https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryDraft/celiac-disease-screening?ds=1&s=celiac%20disease.[13] The focus of the review was on the effectiveness of screening for celiac disease in asymptomatic adults, adolescents, and children on morbidity, mortality, and quality of life. The analytic framework and key questions (KQs) to guide the review are shown in **Figure 1**. The full report includes additional contextual questions (not reviewed systematically) on the prevalence and natural history of subclinical or silent celiac disease.

Data Sources and Searches

The Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Ovid MEDLINE databases were searched from 1991, 2005, and 1946, respectively, to June 14, 2016, for relevant studies and systematic reviews. The search strategies are listed in the eMethods in the Supplement. Reference lists of relevant articles were also reviewed.

Study Selection

Two reviewers independently evaluated each study to determine inclusion eligibility. Studies were selected on the basis of inclusion and exclusion criteria developed for each KQ. For screening and diagnosis, the population of interest was asymptomatic adults, adolescents, or children 3 years or older without known celiac disease who had not sought evaluation for possible celiac disease. The population included persons at higher risk because of family history or presence of conditions associated with celiac disease, such as type 1 diabetes mellitus, autoimmune thyroiditis, or Down syndrome, as well as persons not known to be at higher risk. For treatment, the population of interest was asymptomatic persons with screen-detected celiac disease. Studies of mildly symptomatic patients were also included if no studies were available in asymptomatic populations.

Screening tests were serologic tests or questionnaires. Included were randomized trials, cohort studies, and case-control studies performed in primary care or primary care–applicable settings of screening vs no screening, targeted vs universal screening, treatment vs no treatment, and immediate vs delayed treatment that reported morbidity (including clinical outcomes related to nutritional deficiencies and gastrointestinal symptoms), cancer incidence, mood and anxiety, child growth outcomes, infection rates, quality of life, mortality, or harms associated with screening or treatment. For diagnostic accuracy, cohort and cross-sectional studies that compared screening tests against intestinal biopsy as the reference standard were included. The Marsh classification system categorizes biopsy findings based on the presence of intraepithelial lymphocytosis (Marsh 1 or greater), crypt hyperplasia (Marsh 2 or greater), and villous atrophy (Marsh 3 or greater).[15] The presence of villous atrophy (Marsh 3 or 4) is considered the hallmark of celiac disease, with Marsh 1 and 2 more equivocal.

Studies reporting only intermediate outcomes such as laboratory values for nutritional or other deficiencies and studies that evaluated diagnostic accuracy using a case-control design were excluded. To summarize the diagnostic accuracy of screening tests in populations not restricted to asymptomatic persons, good-quality systematic reviews published since 2015 were also included. The selection of literature is summarized in the literature flow diagram (**Figure 2**).

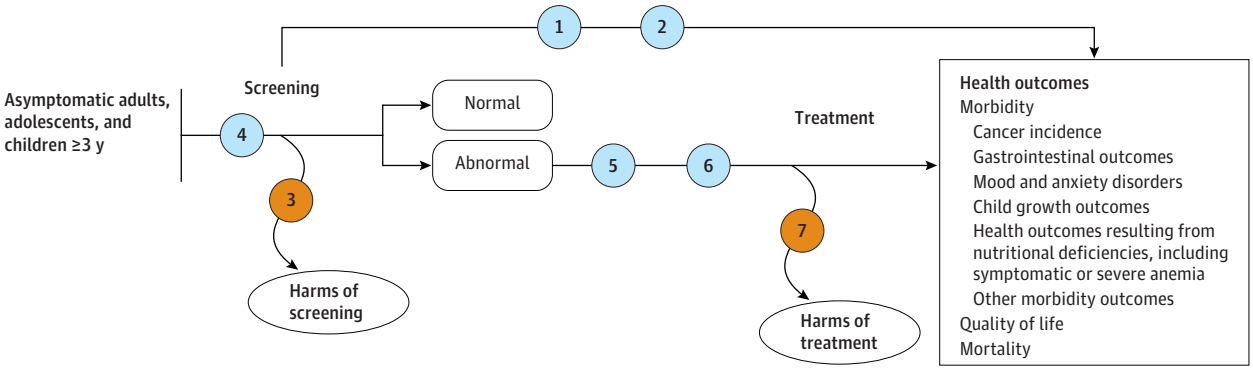
Data Extraction and Quality Assessment

One investigator extracted details about each article's study design, patient population, setting, screening method, treatment regimen, analysis, follow-up, and results. A second investigator reviewed data abstraction for accuracy. Two investigators independently applied criteria developed by the USPSTF[16] to rate the quality of each study as good, fair, or poor. The quality assessment criteria are reported in the eMethods in the Supplement. Discrepancies were resolved through consensus.

Data Synthesis and Analysis

The aggregate internal validity (quality) of the body of evidence for each KQ (good, fair, poor) was assessed using methods developed by the USPSTF, based on the number, quality, and size of studies; consistency of results between studies; and directness of evidence.[16] There were too few studies to perform meta-analysis.

Figure 1. Analytic Framework and Key Questions



Key questions

1. What is the effectiveness of screening vs not screening for celiac disease in asymptomatic adults, adolescents, or children on morbidity, mortality, or quality of life?
2. What is the effectiveness of targeted vs universal screening for celiac disease in asymptomatic adults, adolescents, or children on morbidity, mortality, or quality of life? (Targeted screening refers to testing in patients with family history or other risk factors for celiac disease.)
3. What are the harms of screening for celiac disease?
4. What is the accuracy of screening tests for celiac disease?
5. Does treatment of screen-detected celiac disease lead to improved morbidity, mortality, or quality of life compared with no treatment?
6. Does treatment of screen-detected celiac disease lead to improved morbidity, mortality, or quality of life compared with treatment initiated after clinical diagnosis?
7. What are the harms associated with treatment of celiac disease?

Evidence reviews for the US Preventive Services Task Force (USPSTF) use an analytic framework to visually display the key questions that the review will address to allow the USPSTF to evaluate the effectiveness and safety of a preventive service. The questions are depicted by linkages that relate interventions and outcomes. Further details are available from the USPSTF procedure manual.[14]

Results

Searches identified 3036 citations, of which 2819 were excluded at the title and abstract stage. Full-text articles were retrieved for the remaining 217 articles, from which 213 were excluded (see Figure 2 for detailed reasons for exclusion of full-text articles). A total of 4 studies (1 systematic review and 3 primary studies) met inclusion criteria.

Screening

Key Question 1. What is the effectiveness of screening vs not screening for celiac disease in asymptomatic adults, adolescents, or children on morbidity, mortality, or quality of life?

Key Question 2. What is the effectiveness of targeted vs universal screening for celiac disease in asymptomatic adults, adolescents, or children on morbidity, mortality, or quality of life?

Key Question 3. What are the harms of screening for celiac disease?

No studies on the effects of screening vs no screening or targeted vs universal screening on morbidity, mortality, quality of life, or harms in asymptomatic adults, adolescents, or children were identified.

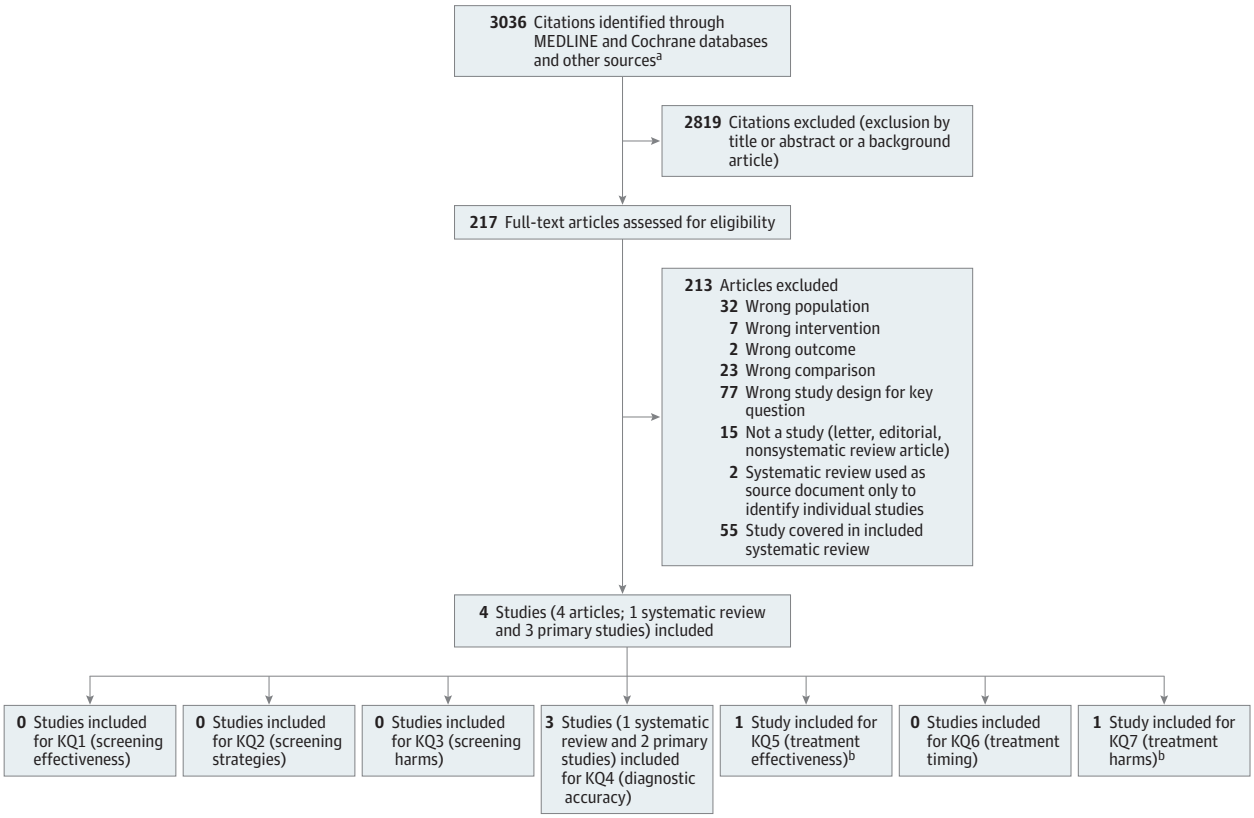
Test Accuracy

Key Question 4. What is the accuracy of screening tests for celiac disease?

A recent good-quality systematic review on the diagnostic accuracy of tests for celiac disease compared with a reference standard of endoscopic duodenal biopsy included 56 original studies and 12 previous systematic reviews (**Table 1**; eTable 1 in the Supplement).[17] Sample sizes ranged from 62 to more than 12 000 participants. Three studies in the review focused on diagnostic accuracy of testing in children, adolescents, or both[18-20]; 6 evaluated a mixed population of children and adults[21-26]; and the remainder focused on testing in adults. One study was conducted in the United States,[27] 5 in the Middle East,[22,24,28-30] 1 in India,[31] 1 in Argentina,[32] and the rest in Europe.[18-21,23,25,26,33-40] Only 2 studies reported diagnostic accuracy in asymptomatic persons.[19,22]

Overall, including studies of persons with symptoms or in whom symptom status was not described, the systematic review found high strength of evidence that tissue transglutaminase (tTG) immunoglobulin A (IgA) was associated with high accuracy for diagnosis of celiac disease (sensitivity and specificity both

Figure 2. Literature Search Flow Diagram



[a] Cochrane databases include the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews. Other sources include reference lists of relevant articles, systematic reviews, and expert suggestions.

[b] The same study is included for key questions 5 and 7.

>90%), and endomysial antibodies (EMA) IgA tests were associated with high specificity, based on consistent results from prior systematic reviews and new studies. For tTG IgA, the pooled sensitivity based on new studies was 92.8% (95% CI, 90.3% to 94.8%) and specificity 97.9% (95% CI, 96.4% to 98.8%), for a positive likelihood ratio (LR) of 45.1 (95% CI, 25.1 to 75.5) and negative LR of 0.07 (95% CI, 0.05 to 0.10). For EMA IgA testing, the pooled sensitivity based on new studies was 73.0% (95% CI, 61.0% to 83.0%) and specificity 99.0% (95% CI, 98.0% to 99.0%), for a positive LR of 65.6 (95% CI, 35.6 to 120.8) and negative LR of 0.28 (95% CI, 0.17 to 0.41). Results for deamidated gliadin peptide (DGP) IgA tests indicated somewhat weaker LRs. For DGP IgA, the pooled sensitivity was 87.8% (95% CI, 85.6% to 89.9%) and specificity was 94.1% (95% CI, 92.5% to 95.5%), for a positive LR of 13.3 (95% CI, 9.6 to 18.4) and negative LR of 0.12 (95% CI, 0.08 to 0.18). For video capsule endoscopy, the pooled sensitivity was 89.0% (95% CI, 82.0% to 94.0%) and specificity 95.0% (95% CI, 89.0% to 99.0%), for a positive LR of 12.9 (95% CI, 2.9 to 57.6) and negative LR of 0.16 (95% CI, 0.10 to 0.25).

Three studies in the systematic review compared the accuracy of tests by age group.[20,23,39] Sensitivities and specificities were generally similar across age groups, with the exception of 1 study that reported specificity of 26% among persons 18 years or younger for the DGP IgA test.[20] Sensitivities were somewhat lower for adults than for children, but differences were slight.

Only 2 studies included in the systematic review reported diagnostic accuracy in asymptomatic persons (**Table 2**; eTable 2 in the Supplement).[19,22] A small (n = 62), fair-quality study of patients in Iraq (mean age, 23 years) with type 1 diabetes mellitus and without symptoms or a family history of celiac disease evaluated IgA tTG, IgG tTG, IgA EMA, and IgA and IgG antigliadin antibodies assays.[22] The prevalence of celiac disease based on biopsy was 11.3% (7/62); sensitivities ranged from 57% for the IgG tTG test to 71% for the IgA tTG and IgA EMA tests, resulting in positive predictive values of 50.0% to 71.4%; specificities were similar across tests, ranging from 93% to 98%, for negative predictive values of 94.4% to 96.4%. The other study was of fair quality and reported diagnostic accuracy of the combination of IgA tTG and IgA EMA in a subgroup of 158 asymptomatic Czech children and adolescents aged 16 months to 19 years at higher risk for celiac disease because they had a first-degree relative with celiac disease or had an associated disease such as type 1 diabetes mellitus or autoimmune thyroiditis.[19] The prevalence of Marsh 2 or 3 biopsy findings was 78.5% (124/158), with sensitivity of 67% and specificity of 83% for the combination of IgA tTG greater than 10 times the upper limit of normal and positive IgA EMA result.

Table 1. Key Question 4: Systematic Review of Diagnostic Accuracy Studies

Source, Quality	Aim	Databases Searched; Literature Search Dates; Other Data Sources	Eligibility Criteria	No. of Studies and Sample Size	Characteristics of Identified Articles			Pooled Results, Measure (95% CI)
					Study Design	Populations	Interventions	
Maglione et al,[17] 2016 Good	To assess evidence on comparative accuracy and safety of tests used for the diagnosis of celiac disease (serologic tests, HLA typing, video capsule endoscopy, and endoscopic duodenal biopsy	PubMed, EMBASE, Cochrane Library, Web of Science Search dates: 1990 to 2015 Unpublished data from manufacturers of serologic tests	Controlled trials, prospective and retrospective cohorts, case-control studies, and case series that used endoscopy with duodenal biopsy as the reference standard; applied the index test and reference standard in all participants; enrolled a consecutive or random sample; included ≥300 patients (unless the study assessed a special population); reported sensitivity and specificity (or data that allowed calculation)	56 studies and 12 prior systematic reviews (27 studies and 10 systematic reviews addressed comparative diagnostic accuracy; 23 of the studies [newly published] not included in the systematic reviews) (Range, 62 to 12 000)	Systematic reviews: 10 Controlled trials: 0 Cohort: 16 Case-control: 7	United States, 1; United Kingdom, 3; Middle East, 5; India, 1; Argentina, 1; Europe, 12 Race/ethnicity rarely described. All studies included symptomatic patients or patients with risk factors or family history of celiac disease. 6 studies were conducted in children and/or adolescents, and an additional 3 studies included a mixed population of children and adults.	Video capsule endoscopy: 2 systematic reviews; tTG: 3 systematic reviews and 16 original studies (3 in special populations); EMA: 2 systematic reviews and 5 original studies; DGP: 3 systematic reviews and 2 original studies; HLA antigen typing: no evidence in general population (2 studies in special populations); Algorithms: 8 original studies	**Video capsule endoscopy** Sensitivity (%): 89.0 (82.0-94.0) Specificity (%): 95.0 (89.0-99.0) LR+: 12.9 (2.9-57.6) LR−: 0.16 (0.10-0.25) **tTG** Sensitivity (%): 92.8 (90.3-94.8) Specificity (%): 97.9 (96.4-98.8) LR+: 45.1 (25.1-75.5) LR−: 0.07 (0.05-0.10) **EMA** Sensitivity (%): 73.0 (61.0-83.0) Specificity (%): 99.0 (98.0-99.0) LR+: 65.6 (35.6-120.8) LR−: 0.28 (0.17-0.41) **DGP** Sensitivity (%): 87.8 (85.6-89.9) Specificity (%): 94.1 (92.5-95.5) LR+: 13.3 (9.6-18.4) LR−: 0.12 (0.08-0.18) **HLA typing** No evidence Algorithms using ≥1 tests Insufficient evidence due to heterogeneity **Conclusions:** video capsule endoscopy, tTG, EMA, and DGP all highly accurate. Additional studies needed on accuracy of algorithms and accuracy of testing in special populations.

Abbreviations: AHRQ, Agency for Healthcare Research and Quality; DGP, deaminated gliadin peptide; EMA, endomysial antibodies; LR−, negative likelihood ratio; LR+, positive likelihood ratio; tTG, antitissue transglutaminase.

Table 2. Key Question 4: Diagnostic Accuracy Studies in Asymptomatic Populations

Source, Quality[a]	Screening Tests	Setting	Age of Enrollees	No.	Marsh Classification, No./Total (%)[b]	Patients	% (95% CI)[c]	
							Sensitivity	Specificity
Mansour,[22] 2011 Fair	IgA tTG IgG tTG IgA EMA IgA AGA IgG AGA	University hospital, Iraq	Mean age, 23.4 (range, 8-42 y)	62	Marsh 3a-c: 7/62 (11.3)	Patients with type 1 diabetes, no symptoms associated with celiac disease, and no family history of celiac disease or thyroid disorders	IgA tTG: 71 (29-96) IgG tTG: 57 (18-90) IgA EMA: 71 (29-96) IgA AGA: 57 (18-90) IgG AGA: 57 (18-90)	IgA tTG: 93 (82-98) IgG tTG: 93 (82-98) IgA EMA: 96 (88-100) IgA AGA: 98 (90-100) IgG AGA: 98 (90-100)
Nevora,[19] 2014 Fair	IgA tTG IgA EMA	Single pediatric department, Czech Republic	Range, 16 mo-19 y	345 (158 asymptomatic)	Marsh 2 or 3, asymptomatic: 124/158 (78.5) 2 or 3, all children: 263/345 (76)	Children and adolescents examined for suspected celiac disease	IgA tTG >10× ULN and positive EMA test: 67 First-degree relatives (n = 32): 70 Type 1 diabetes mellitus (n = 40): 64	IgA tTG >10× ULN and positive EMA test: 83 First-degree relatives (n = 32): 81 Type 1 diabetes mellitus (n = 40): 93

Abbreviations: AGA, antigliadin antibodies; AUROC, area under the receiver operating characteristic curve; EMA, endomysial antibodies; NR, not reported; tTG, tissue transglutaminase; ULN, upper limit of normal.

[a] Both studies were of cross-sectional design, with biopsy as the reference standard.

[b] The Marsh classification system categorizes biopsy findings based on the presence of intraepithelial lymphocytosis (Marsh 1 or greater), crypt hyperplasia (Marsh 2 or greater), and villous atrophy (Marsh 3 or greater).[15] The presence of villous atrophy (Marsh 3 or 4) is considered the hallmark of celiac disease, with Marsh 1 and 2 more equivocal.

[c] Area under the receiver operating characteristic curve not reported by either of the studies in this table.

Results were not reported for the subgroup of patients with Marsh 3 biopsy findings. Sensitivity was 70% and specificity 81% for patients screened because they had a first-degree relative (n = 32), and sensitivity was 64% and specificity 93% for patients with type 1 diabetes mellitus (n = 40).

Treatment of Screen-Detected Celiac Disease

Key Question 5. Does treatment of screen-detected celiac disease lead to improved morbidity, mortality, or quality of life compared with no treatment?

One fair-quality trial (n = 40) evaluated a gluten-free vs normal gluten-containing diet in asymptomatic adults (median age, 42 years) diagnosed with celiac disease through screening of relatives of persons with celiac disease (**Table 3**, panels A and B; eTable 3 in the Supplement).[41] Diagnosis of celiac disease was based on a positive serum EMA test result. Although biopsy was performed, histopathological findings of celiac disease were not required for study entry, and researchers were blinded to biopsy results until completion of the trial. At baseline, the mean ratio of villous height to crypt depth was 1.0 in the gluten-free diet group and 0.8 in the non–gluten-free diet group, indicating presence of villous atrophy; 2 patients in each group had a normal ratio of villous height to crypt depth (>2.0).

At 1 year, participants on a gluten-free diet reported significant improvements in total gastrointestinal symptoms vs a non–gluten-free diet based on the overall Gastrointestinal Symptoms Ratings Scale (difference in mean change, −0.4 on a 1 [no symptoms] to 7 [severe symptoms] scale [95% CI, −0.7 to −0.1]), as well as on the diarrhea (difference in mean change, −0.6 [95% CI, −1.1 to 0.0]), indigestion (difference in mean change, −0.7 [95% CI, −1.1 to −0.2]), and reflux (difference in mean change, −0.5 [95% CI, −0.9 to −0.1]) subscales, with no differences on the constipation or abdominal pain subscales (all subscales were Likert scales ranging from 1 [no symptoms] to 7 [severe symptoms]). The gluten-free diet group also reported greater improvement on the anxiety subscale of the Psychological General Well-Being Scale (difference in mean change, 1.6 [95% CI, 0.4 to 2.8] on a scale of 1 [extremely bothered by nervousness or your "nerves"] to 6 [not at all bothered]), with no differences on the depression, well-being, self-control, general health, or vitality subscales. There were no differences in any subscale of the 36-Item Short Form Health Survey aside from social functioning, which was worse in the gluten-free diet group (difference in mean change, −8.3 [95% CI, −15.8 to −0.8] on a scale of 0 [maximum disability in social functioning] to 100 [no disability in social functioning]).

There were no differences between groups in intermediate outcomes such as mean blood hemoglobin level, mean serum total iron level, mean body mass index, mean percent total body fat, or mean lumbar spine or femoral neck bone mineral density. After 2 years, more than 90% of participants reported adherence to the gluten-free diet, and greater improvements in histopathological findings were observed in the gluten-free diet group at 1 year compared with the non–gluten-free diet group.

A recent randomized trial that screened persons with a first- or second-degree relative with celiac disease and randomized patients to immediate notification and initiation of a gluten-free diet vs no notification or initiation of a gluten-free diet was terminated, with no results available.[42] Three small, observational

Table 3. Key Questions 5 and 7: Randomized Clinical Trial of Screen-Detected Treatment—Study Characteristics and Outcome Data[a]

Source, Quality	Sample Sizes	Interventions and Patient Characteristics	Inclusion/ Exclusion Criteria	Outcomes Assessed	Clinical Health Outcomes[b]
Kurppa et al,[41] 2014; Fair	Screened: 3031 at-risk volunteers Eligible: 40 Enrolled: 40 Analyzed: 40 (20 in each group) Withdrawal or loss to follow-up: 0	A (gluten diet) vs B (GFD)[c] Median age, 42 (range, 23-62) vs 42 (21-74) y Women: 25% vs 45% Hypothyroidism: 10% vs 5% Other chronic condition: 35% vs 35% Osteoporotic fracture: 0% vs 0% Women: infertility or frequent miscarriages: 20% vs 11% Median age at menarche (range): 13 (13-15) vs 13 (9-14) y	Targeted screening (relatives of celiac patients). Included EMA-positive adults (18-75 y) who considered themselves asymptomatic (defined as absence of: abdominal pain [>3 episodes over ≥3 mo interfering with function], constipation [<3 bowel movements/wk or difficulty during defecation], diarrhea [≥3 loose stools/d], and extraintestinal symptoms such as joint pain, blistering rash, or unexplained neurologic symptoms, and alarm symptoms including unexplained severe weight loss, vomiting, frequent or continuous fever, or rectal bleeding). Celiac disease was defined as the presence of positive EMA and gluten-dependent enteropathy. Exclusions: previous diagnosis of celiac disease, age <18 y, evident clinical symptoms, dietary gluten restriction, severe contemporary illness, immunosuppressive medication, ongoing or planned pregnancy.	Serology Celiac-related genotyping GSRS: 7-point Likert scale, higher score indicates more severe symptoms PGWB: 6-point Likert scale, higher score indicates better health-related quality of life SF-36: 0-100, higher score indicates better health-related quality of life VAS: 0-100, higher score indicates better subjective perception of health Laboratory parameters BMD Body composition Small bowel mucosal morphology and inflammation	**Gastrointestinal symptoms after 1 y, difference in mean change (95% CI):** GSRS: Total, −0.4 (−0.7 to −0.1); *P* = .003; favors GFD Diarrhea: −0.6 (−1.1 to 0.0); *P* = .052; favors GFD Indigestion: −0.7 (−1.1 to −0.2); *P* = .006; favors GFD Constipation: −0.1 (−0.5 to 0.3); *P* = .325 Abdominal pain: −0.2 (−0.5 to 0.2); *P* = .126 Reflux: −0.5 (−0.9 to −0.1); *P* = .050; favors GFD **Psychological general well-being after 1 y, difference in mean PGWB change (95% CI):** Anxiety: 1.6 (0.4 to 2.8); *P* = .025; favors GFD Depression: 0.3 (−0.5 to 1.2); *P* = .281 Well-being: 0.5 (−1.0 to 2.0): *P* = .700 Self-control: 0.3 (−0.7 to 1.4); *P* = .775 General health: 0.7 (−1.0 to 2.4); *P* = .532 Vitality: 0.4 (−1.5 to 2.2); *P* = .670 **SF-36 after 1 y, difference in mean change (95% CI):** Physical functioning: −2.8 (−8.2 to 2. 6); *P* = .299 Role limitations due to physical problems: 2.3 (−12.4 to 17); *P* = .749 Role limitations due to emotional problems: 7.2 (−12.6 to 27); *P* = .464 Vitality: 6.0 (−4.3 to 16.4); *P* = .245 Mental health: 2.6 (−3.8 to 8.9); *P* = .414 Social functioning: −8.3 (−15.8 to −0.8); *P* = .031; favors gluten group Bodily pain: 0.8 (−9.8 to 11.4); *P* = .881 General health: 2.8 (−7.1 to 12.7); *P* = .568 VAS: Improved in the GFD group (*P* = .017) **Laboratory parameters:** Blood hemoglobin, mean (SD), g/dL: A. Baseline, 14.3 (1.4); change after 1 y, −0.2 (0.6) B. Baseline, 14.4 (1.6); change after 1 y, −0.2 (0.7) Difference between groups, mean (95% CI): 0.0 (−0.4 to 0.4), *P* = .902 Serum total iron, mean (SD), μmol/L: A. Baseline, 17.3 (5.7); change after 1 y, 2.8 (6.8) B. Baseline, 20.0 (8.6); change after 1 y, 0.3 (7.2) Difference between groups, mean (95% CI): −2.5 (−7.0 to 2.1), *P* = .288 **Body composition:** BMI, mean (SD)[d]: A. Baseline, 26.4 (3.7); change after 1 y, −0.3 (1.0) B. Baseline, 27.0 (6.8); change after 1 y, 0.0 (1.2) Difference between groups, mean (95% CI): 0.3 (−0.5 to 1.0), *P* = .451 Percent total body fat, mean (SD): A. Baseline, 28.9 (8.2); change after 1 y, −0.6 (2.4) B. Baseline, 34.0 (8.9); change after 1 y, −1.2 (3.4) Difference between groups, mean (95% CI): −0.5 (−2.4 to 1.4), *P* = .600 **BMD, lumbar spine, mean (SD), g/cm^2:** A. Baseline, 1.17 (0.21); change after 1 y, −0.01 (0.03) B. Baseline, 1.17 (0.19); change after 1 y, 0.00 (0.02) Difference between groups, mean (95% CI), 0.01 (−0.01 to 0.02); *P* = .338 BMD, femur neck, mean (SD), g/cm^2: A. Baseline, 1.00 (0.12); change after 1 y, −0.1 (0.03) B. Baseline, 0.97 (0.14); change after 1 y, 0.00 (0.02) Difference between groups, mean (95% CI): 0.01 (−0.01 to 0.03), *P* = .182

Abbreviations: BMD, bone mineral density; BMI, body mass index; EMA, endomysial antibodies; GFD, gluten-free diet; GSRS, Gastrointestinal Symptoms Rating Scale; PGWB, Psychological General Well-Being; SF-36, 36-Item Short Form Health Survey; VAS, visual analog scale.

[a] Study was conducted at a single center in Finland. Duration of follow-up was 1 year; there were no withdrawals "as a result of major symptoms or complications."

[b] "Favors" language included only for statistically significant results.

[c] One person in group A started a gluten-free diet soon after randomization but was analyzed in the gluten group owing to the intention-to-treat analysis.

[d] Calculated as weight in kilograms divided by height in meters squared.

Table 4. Summary of Evidence

Key Question Topic	No. of Studies (Study Design), Sample Size	Summary of Findings (Including Consistency and Precision)	Applicability	Limitations (Including Reporting Bias)	Overall Study Quality
Key question 1: Benefits of screening vs no screening	No studies				
Key question 2: Benefits of targeted vs universal screening	No studies				
Key question 3: Harms of screening	No studies				
Key question 4: Accuracy of screening tests	1 systematic review (56 diagnostic accuracy studies and 12 other systematic reviews) n = 62 to >12 000	One good-quality systematic review found tTG antibody tests associated with high sensitivity and specificity in populations not restricted to asymptomatic persons. Based on new studies, the pooled sensitivity (%) in the systematic review was 92.8 (95% CI, 90.3-94.8) and specificity (%) was 97.9 (95% CI, 96.4-98.8), for a LR+ of 45.1 (95% CI, 25.1-75.5) and LR+ of 0.07 (95% CI, 0.05-0.10). EMA antibody tests were also associated with strong likelihood ratios. Evidence was consistent and precise.	Moderate Most studies in non-US settings and included persons with symptoms.	Only 2 studies included asymptomatic persons.	Fair
	2 diagnostic accuracy studies in asymptomatic persons n = 220	Limited evidence from 2 studies of serologic testing in asymptomatic, high-risk children and younger adults reported lower sensitivity (57%-71%); specificity ranged from 83%-98%. Evidence was imprecise; consistency could not be evaluated because the populations were heterogeneous.	High Non-US setting	Fair-quality studies. No evidence of reporting bias.	Poor
Key question 5: Benefits of screen-detected treatment vs no treatment	1 trial n = 40	One small, fair-quality trial of screen-detected, asymptomatic adults found a gluten-free diet associated with small improvements in gastrointestinal symptoms (less than 1 point on a 1-7 scale) vs no gluten-free diet after 1 y, but there were no changes on most quality-of-life outcomes. Evidence was imprecise; consistency could not be determined (1 study).	Moderate Non-US setting. Some patients did not have biopsy findings of celiac disease or minimal histologic changes.	Fair-quality study. No evidence of reporting bias.	Poor
Key question 6: Benefits of screen-detected treatment vs treatment initiated after clinical diagnosis	No studies				
Key question 7: Harms of treatment	1 trial n = 40	The trial included for key question 5 reported no withdrawals "as a result of major symptoms or complications." No other study on harms of gluten-free vs non-gluten-free diet in persons with screen-detected celiac disease was identified. Evidence was imprecise; consistency could not be determined (1 study).	High Non-US setting	Fair-quality study. No evidence of reporting bias.	Poor

Abbreviations: EMA, endomysial antibodies; LR−, negative likelihood ratio; LR+, positive likelihood ratio; tTG, antitissue transglutaminase.

studies on effects of a gluten-free diet in persons with asymptomatic celiac disease were excluded because they lacked a gluten-containing diet group for comparison.[43-45] In these studies, there were no clear associations between the initiation of gluten-free diet and quality of life, although 1 study[44] found increased worry about health following initiation of a gluten-free diet and 1 study[45] reported small improvements in gastrointestinal symptoms.

Key Question 6. Does treatment of screen-detected celiac disease lead to improved morbidity, mortality, or quality of life compared with treatment initiated after clinical diagnosis?

No study on the effectiveness of treatment of screen-detected celiac disease compared with treatment initiated after clinical diagnosis on morbidity, mortality, or quality of life was identified.

Key Question 7. What are the harms associated with treatment for celiac disease?

The trial by Kurppa et al[41] of gluten-free diet included for KQ5 reported no withdrawals "as a result of major symptoms or complications." No other study on harms of gluten-free vs non-gluten-free diet in persons with screen-detected celiac disease were identified.

Discussion

Table 4 summarizes the evidence reviewed for this update. No studies of screening vs no screening or targeted vs universal screening for celiac disease in adults, adolescents, or children aged 3 years or older were identified. Although serologic tests for celiac disease used in screening appear to be highly accurate and study designs were appropriate, almost all studies on diagnostic accuracy evaluated populations with symptoms of celiac disease or in whom symptom status was not reported. Two studies that specifically evaluated asymptomatic patients at high risk for celiac disease based on family history or presence of conditions associated with celiac disease reported lower sensitivity and inconsistent specificity.[19,22] Neither of these studies were conducted in the United States. Only 1 Finland-based randomized trial evaluated the effectiveness of gluten-free diet vs no gluten-free diet in asymptomatic adults with screen-detected celiac disease.[41] That trial found initiation of a gluten-free diet in screen-detected, asymptomatic adults associated with improved gastrointestinal symptoms, although effects were relatively small (<1 point on a scale of 1-7). There were no effects on most measures of quality of life; no harms resulting in withdrawal from the diet occurred. In this study, patients had a first-degree relative with celiac disease and were diagnosed on the basis of serologic testing. Histologic findings of celiac disease were not required for entry. Although most patients had some degree of villous atrophy at baseline, it is possible that this trial could have underestimated benefits of treatment in patients with histologically proven celiac disease. No study evaluated the effects of immediate initiation of a gluten-free diet vs initiation delayed until the development of symptoms in asymptomatic persons diagnosed with celiac disease.

A recent randomized trial of immediate notification and initiation of a gluten-free diet for screen-detected celiac disease vs no notification or gluten-free diet was terminated; we were unable to determine reasons for study termination.[42] Three small, observational studies on effects of a gluten-free diet for asymptomatic celiac disease that did not meet inclusion criteria because they lacked a gluten-containing diet comparison group found no clear associations with quality of life.[43-45]

The major limitation of this review is the lack of evidence to address the KQs. In addition, although numerous studies evaluated the diagnostic accuracy of tests for celiac disease in patients who were not asymptomatic, the applicability of findings to screening settings is uncertain. Meta-analysis was not possible, and publication bias could not be formally assessed. Inclusion was restricted to English-language articles, but no non–English-language articles were found on benefits or harms of screening or treatment that appeared to meet inclusion criteria. Although during the review of abstracts some non–English-language articles were identified that assessed diagnostic accuracy, none were clearly conducted in asymptomatic populations.

An emerging issue is the treatment of celiac disease based on serologic testing, without histologic confirmation. The number of patients who are diagnosed with celiac disease or initiate a gluten-free diet based on serologic testing alone is unknown but may be increasing in clinical practice, despite guideline recommendations to obtain histologic confirmation prior to initiation of treatment. A related issue is how to classify persons with positive serologic findings but negative or nondiagnostic findings on biopsy and manage their care. The likelihood that such patients will go on to develop overt celiac disease requires further investigation and has important implications for understanding effects of treatment. Although there continues to be research on pharmacological treatments for celiac disease,[46-49] such treatments are considered an adjunct to a gluten-free diet, which remains the mainstay of therapy.

Additional research is needed to address all of the KQs addressed in this report. For screening, trials of screening vs no screening that evaluate clinical outcomes are needed. Trials that target high-risk populations (based on family history or presence of conditions associated with celiac disease) would likely provide a higher yield of screen-detected persons than trials that screen persons at lower or average risk, resulting in greater statistical power to detect effects, and might be more informative for an initial screening study. Additional studies are needed to determine the accuracy of serologic testing in asymptomatic persons. Trials are also needed on the effects of initiation of a gluten-free diet vs no gluten-free diet in screen-detected individuals and on the effects of immediate initiation at diagnosis vs initiation delayed until the development of symptoms. The in-progress Celiac Disease and Diabetes-Dietary Intervention and Evaluation Trial (CD-DIET) (ClinicalTrials.gov Identifier: NCT01566110), which involves screening of children and adults with type 1 diabetes mellitus for asymptomatic celiac disease followed by randomization to a gluten-free or no gluten-free diet, is designed to assess outcomes (including diabetes control, bone mineral density, and health-related quality of life) over 1 year and should help clarify effects of screening in higher-risk individuals.[50] Ideally, future studies would provide information on long-term outcomes related to nutritional deficiencies such as osteoporotic fractures, cancer, and mortality. Because of the uncertain natural history of positive serologic findings without histologic changes, trials should focus on patients with histologic findings of celiac disease or report analyses stratified according to baseline histologic findings. Trials should evaluate populations across the age spectrum, including children, adolescents, and adults, because celiac disease can be diagnosed in any of these age groups.

Additional research is also needed to better understand the natural history of subclinical and silent celiac disease, including the proportion of patients who develop symptoms, the proportion who develop complications, and the proportion in whom serologic findings, histologic findings, or both resolve without treatment. Some data suggest that subclinical or silent celiac disease is associated with a lower risk of developing complications than symptomatic celiac disease.

Conclusions

Although some evidence was found regarding diagnostic accuracy of tests for celiac disease, little or no evidence was identified to inform most of the key questions related to benefits and harms of screening for celiac disease in asymptomatic individuals. More research is needed to understand the effectiveness of screening and treatment for celiac disease, accuracy of screening tests in asymptomatic persons, and optimal screening strategies.

ARTICLE INFORMATION

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