Evidence Synthesis

Number 144

Screening for Celiac Disease: A Systematic Review for the U.S. Preventive Services Task Force

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
5600 Fishers Lane
Rockville, MD 20857
www.ahrq.gov

Contract No. HHSA-290-2012-00015-I, Task Order No. 4

Prepared by:
Pacific Northwest Evidence-Based Practice Center
Oregon Health & Science University
3181 SW Sam Jackson Park Road
Portland, OR 97239
www.ohsu.edu/epc

Investigators:
Roger Chou, MD
Ian Blazina, MPH
Christina Bougatsos, MPH
Katherine Mackey, MD
Sara Grusing, BA
Shelley Selph, MD, MPH

AHRQ Publication No. 14-05215-EF-1
March 2017

This report is based on research conducted by the Pacific Northwest Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (HHSA-290-2012-00015-I, Task Order No. 4). The findings and conclusions in this document are those of the authors, who are responsible for its contents, and do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information (i.e., in the context of available resources and circumstances presented by individual patients).

This report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

Acknowledgements

The authors acknowledge AHRQ Medical Officers Tracy Wolff, MD, MPH, and Karen Lee, MD, MPH, as well as current and former members of the U.S. Preventive Services Task Force who contributed to topic discussions.

Suggested Citation

Chou R, Blazina I, Bougatsos C, Mackey K, Grusing S, Selph S. Screening for Celiac Disease: A Systematic Review for the U.S. Preventive Services Task Force. Evidence Synthesis No. 144. AHRQ Publication No. 14-05215-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2017.

Structured Abstract

Background: Unrecognized celiac disease may have adverse effects on morbidity and mortality.

Purpose: To review the evidence on screening for celiac disease in asymptomatic adults, adolescents, and children age 3 years or older for the U.S. Preventive Services Task Force.

Data Sources: Ovid MEDLINE, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews (to mid-June 2016).

Study Selection: Randomized clinical trials, cohort studies, and case-control studies of screening versus no screening, one screening strategy versus another, treatment versus no treatment, or immediate versus delayed treatment that evaluated clinical outcomes; and studies on diagnostic accuracy of serologic tests for celiac disease.

Data Extraction: One investigator abstracted data, a second checked data for accuracy, and two investigators independently assessed study quality using predefined criteria.

Data Synthesis (Results): We identified no trials of screening for celiac disease. One recent, good-quality systematic review found serologic tests to be accurate for diagnosing celiac disease, but two studies conducted in asymptomatic populations reported lower sensitivity than in studies not restricted to asymptomatic populations. One fair-quality, small (n=40) Finnish treatment trial of screen-detected, asymptomatic adults with positive serologic findings found initiation of a gluten-free diet associated with small improvement in gastrointestinal symptoms versus no gluten-free diet (<1 point on a 7-point scale) at 1 year, with no differences on most measures of quality of life. No withdrawals due to adverse events occurred during the trial.

Limitations: Limited or no evidence for all key questions; limited to English-language studies.

Conclusions: More research is needed to understand the effectiveness of screening for and treatment of celiac disease in asymptomatic adults, adolescents, and children; accuracy of screening tests; and optimal screening strategies.

Table of Contents

Figure

Tables

Appendixes

Chapter 1. Introduction

Purpose and Previous U.S. Preventive Services Task Force Recommendation

This report, commissioned by the Agency for Healthcare Research and Quality (AHRQ), will be used by the U.S. Preventive Services Task Force (USPSTF) to develop a recommendation on screening for celiac disease in adults, adolescents, and children age 3 years or older. This topic has not previously been reviewed by the USPSTF.

Condition Definition

Celiac disease is a multisystem autoimmune disorder in genetically predisposed persons that is triggered by ingestion of dietary gluten. Gluten is a protein complex found in wheat, rye, and barley. In persons with celiac disease, ingestion of gluten causes immune-mediated inflammatory damage to the mucosa of the small intestine and subsequent malabsorption of nutrients. Celiac disease can manifest as both gastrointestinal and nongastrointestinal illness. Other names for the disorder include celiac sprue, gluten-sensitive enteropathy, and nontropical sprue.

Prevalence

A challenge in estimating prevalence of celiac disease is that in a number of studies, diagnosis was based on serologic testing without histologic confirmation, potentially overestimating prevalence of celiac disease due to false-positive serologic tests. However, a systematic review of 38 studies in North America and Western Europe found that celiac disease prevalence was 0.15 to 1.87 percent in studies that included biopsy confirmation of positive serologic tests, and was similar (0.15% to 2.67%) in studies that did not perform biopsy confirmation in all patients; among the three U.S. studies, prevalence ranged from 0.40 to 0.95 percent in adults.[1] In the largest multicenter U.S. study included in the systematic review, overall prevalence of celiac disease diagnosed by endomysial antibody (EMA)-positive serology and confirmed by biopsy (<30%) or human leukocyte antigen (HLA) haplotypes DQ2 and DQ8 among 4,126 average-risk persons was 0.75 percent, with prevalence of 0.95 percent among adults, 0.31 percent among children, 0.72 percent among women, and 0.78 percent among men.[2] Prevalence among minority groups was 0.42 percent; results were not presented for specific minority groups. A screening study for celiac disease using stored sera from a population-based sample of adults age 50 years or older in Minnesota found that the prevalence of undiagnosed celiac disease was 0.8 percent, as defined by initial tissue transglutimase (tTG) immunoglobin (Ig)A testing followed by EMA tests.[3] Median age of those diagnosed was 63 years and 51 percent were women. In a study of 7,798 persons age 6 years or older who participated in the 2009–2010 National Health and Nutrition Examination Survey (NHANES), the prevalence of celiac disease, as defined by positive serology or patient-self report, was 0.71 percent among the general population, 0.76 percent among those age 20 years or older, 0.62 percent among women, and 1.01 percent among

non-Hispanic whites.[4] Some data suggest that the prevalence of celiac disease in the United States has increased over the past several decades for reasons that are not well understood but may be related to changes in dietary gluten.[5-7] (See Contextual Question 1 for prevalence of celiac disease among patients without overt symptoms.)

Etiology, Natural History, and Burden of Disease

Celiac disease is caused by an immune response to dietary gluten in genetically susceptible persons. Specifically, persons with alleles that encode for HLA-DQ2 and DQ8 proteins are at risk for celiac disease. However, many persons with these alleles do not develop celiac disease, meaning that their presence is necessary but not sufficient for disease. Gliadin, the alcohol-soluble fraction of gluten, triggers both adaptive and innate immune system responses causing infiltration of inflammatory cells into the lamina propria and epithelium of the small intestine, resulting in villous atrophy.[8] Inflammatory injury to the small intestine results in loss of absorptive surface area, reduction in digestive enzymes, and impaired absorption of micronutrients, including fat-soluble vitamins and iron. Although some research suggests an association between breastfeeding with delayed introduction of gluten into the infant diet and decreased risk of celiac disease,[9] more recent literature has not found an association between breastfeeding and risk of celiac disease.[10, 11] Gastrointestinal illness may increase the risk of celiac disease in infancy.[8]

Celiac disease affects both children and adults. Seroconversion to antibodies associated with celiac disease may occur at any time, and disease progression can take place over months or years.[12] Data suggest that the average age at celiac disease diagnosis has increased and is now in the fourth to sixth decades of life.[13, 14]

The clinical presentation, severity of symptoms, and natural history of celiac disease varies among both adults and children. *Classic* celiac disease presents with symptoms of malabsorption, such as diarrhea, abdominal pain, and weight loss. In children, classic celiac disease is characterized by onset of gastrointestinal symptoms and impaired growth between ages 6 and 24 months, but this is now an uncommon presentation.[15] Analysis of trends among 590 patients with biopsy-diagnosed celiac disease in New York from 1981 to 2004 found that the percentage presenting with diarrhea decreased from 91.3 percent before 1980 to 37.2 percent after 2000, perhaps due to increased awareness of celiac disease, increased screening in asymptomatic or mildly symptomatic persons, and/or ease of serologic testing.[13] Celiac disease now presents more typically 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.[8] Children may also experience pubertal delay and dental enamel defects.[15]

Another form of celiac disease is *subclinical* disease, or disease that is below the threshold of clinical detection (i.e., without signs or common symptoms sufficient to trigger testing for celiac disease).[16] Persons with subclinical celiac disease may have nonspecific symptoms of celiac disease, such as fatigue, that are not recognized until initiation of a gluten-free diet. *Asymptomatic*, or *silent*, celiac disease refers to persons who have been diagnosed with celiac

disease by serologic testing and intestinal biopsy but do not manifest any common symptoms or signs of celiac disease. *Potential* celiac disease refers to persons with and without symptoms who have positive serology but absent or mild intestinal damage on biopsy. *Latent* celiac disease, a less commonly used term, describes persons previously diagnosed with celiac disease who have normal intestinal mucosa while on a gluten-free diet or those with normal intestinal mucosa while on a gluten-containing diet who later develop celiac disease.[16, 17] The natural history of subclinical, asymptomatic, potential, and latent celiac disease is not well-defined, and it is not entirely clear if they represent progressive stages of celiac disease or distinct subtypes.[18] In an Italian retrospective study of 549 patients with celiac disease, 45.7 percent showed classical, 47.7 percent subclinical, and 6.6 percent silent forms of celiac disease at the time of diagnosis.[19] (See Contextual Question 2 for additional details regarding the natural history of subclinical or silent celiac disease.)

Some evidence suggests that celiac disease is associated with excess mortality, which is primarily attributed to increased risk for intestinal adenocarcinoma and enteropathy-associated T-cell lymphoma.[8, 20] A recent meta-analysis of observational studies from the United States and Europe showed an increased risk for all-cause mortality in persons with celiac disease (odds ratio [OR], 1.24 [95% confidence interval (CI), 1.19 to 1.30]).[20] In a subgroup analysis, patients identified by positive serology alone were also at an increased risk of all-cause mortality (OR, 1.16 [95% CI, 1.02 to 1.31]) and non-Hodgkin lymphoma (OR, 2.55 [95% CI, 1.02 to 6.36]). However, some data suggest that asymptomatic or silent celiac disease is not associated with increased mortality or other complications of celiac disease. A retrospective study of 549 patients with celiac disease diagnosed by intestinal biopsy found that the rate of complications on a gluten-free diet for a mean duration of 7 years, including malignancy, was highest among those with classic celiac disease (5.58%); no patients with silent disease experienced complications.[19]

Nonceliac gluten sensitivity (NCGS) refers to a condition in which persons with symptoms such as abdominal pain and bloating improve with removal of exposure to gluten but do not have diagnostic features of celiac disease and are not thought to be at increased risk of nutritional deficiency states or other complications associated with celiac disease.[17] Because NCGS is defined based on the presence of symptoms rather than on diagnostic tests, it does not meet criteria for screening and is therefore outside the scope of this review. NCGS is associated with a broad range of symptoms that may manifest as heterogeneous subtypes.[21] A recent double-blinded trial of persons thought to have NCGS found no difference in symptoms following randomization and exposure to high-gluten, low-gluten, or nongluten diets, potentially calling into question the underlying concept for this condition.[22]

Risk Factors

A positive family history is a risk factor for celiac disease. The frequency of celiac disease is higher among first- and second-degree relatives of persons with celiac disease, although prevalence estimates range from 5 to 20 percent.[2, 4, 23] Frequency of celiac disease is also higher among persons with other autoimmune diseases, such as type 1 diabetes mellitus, inflammatory luminal gastrointestinal disorders, Down syndrome, Turner's syndrome, IgA deficiency, and IgA nephropathy.[3, 4, 9, 23]

As discussed previously, celiac disease is more commonly diagnosed among adults ages 40 to 60 years and among non-Hispanic whites. Data regarding risk of celiac disease among women is mixed, but several large-scale prevalence studies found that rates of celiac disease are similar among men and women.[2-4] The major genetic risk factor for celiac disease is inheritance of HLA-DQ2 and DQ8 alleles, which is more likely among first- and second-degree relatives of persons with diagnosed celiac disease.[2]

Rationale for Screening/Screening Strategies

Studies in the United States and Europe suggest that celiac disease may be underdiagnosed, based on the prevalence of positive serologic tests (initial tTG antibody tests followed by EMA testing for those with positive or borderline findings) in persons not previously diagnosed with celiac disease.[24] Evidence also suggests that diagnosis of celiac disease is often delayed. A survey of 1,612 patients with celiac disease in the United States found that symptoms were present for a mean of 11 years before diagnosis.[25] Screening might enable earlier initiation of treatment and reduce the burden of morbidity and mortality associated with untreated celiac disease.[9]

Clinical practice guidelines recommend an algorithmic approach to diagnostic testing for celiac disease, starting with the tTG IgA test and further testing based on the probability of disease.[26, 27] The tTG IgA test is the standard method of testing for celiac disease in persons older than age 2 years. The reported sensitivity of the tTG IgA test is about 95 percent and specificity is 95 percent or greater.[26] In patients in whom celiac disease is suspected but IgA deficiency is a consideration, total IgA levels are measured. Alternatively, IgA testing as well as tTG immunoglobulin G (IgG) and/or IgG deamidated gliadin peptide (DGP) tests can be obtained in such patients. Clinical practice guidelines in the United States and Europe recommend intestinal biopsy to confirm the diagnosis of celiac disease (e.g., based on presence of villous atrophy classified as grade 3 or higher on Marsh criteria) and to distinguish celiac disease from other disorders affecting the small intestine.[26, 27] Intestinal biopsy may also be performed if clinical suspicion for celiac disease is high but serologic tests are negative. It has been suggested that a combination of serologic tests could be used to establish celiac disease diagnosis as an alternative to biopsy,[26, 27] but it is unclear how frequently celiac disease is diagnosed in the absence of biopsy in current clinical practice.[28] Rarely, capsule endoscopy is used to establish a diagnosis of celiac disease in patients who are unwilling or unable to undergo upper endoscopy with intestinal biopsy. HLA-DQ2/DQ8 genotyping is not used routinely to diagnose celiac disease but may be used to rule out the disease in cases with equivocal serologic tests and/or small-bowel histologic findings.

Many persons initiate a gluten-free diet prior to consultation with a health care provider, which complicates the diagnosis of celiac disease and may result in false-negative antibody tests or biopsies. Serologic testing may still be obtained depending on the duration of gluten-free diet, or deferred until gluten has been reintroduced into the diet. HLA-DQ2/DQ8 genotyping is sometimes used to exclude celiac disease before having patients undergo a gluten challenge.[26]

Antigliadin antibodies (AGAs) were previously routinely used to diagnose celiac disease but are

no longer recommended due to inferior sensitivity and specificity compared with newer serologic tests. Likewise, intestinal permeability tests, D-xylose, and small bowel follow-through are not recommended to diagnose celiac disease.[26]

Interventions/Treatment

The mainstay of treatment for celiac disease is lifelong adherence to a gluten-free diet.[29] Short-term vitamin and mineral repletion may also be recommended. Removal of gluten from the diet reverses disease manifestations in a majority of patients.[9] However, complete removal of gluten from the diet is a challenge, as gluten is present in a wide variety of foods, and gluten-free foods can be difficult to obtain and expensive. Nonadherence among patients is also common. A systematic review reported rates of strict adherence to a gluten-free diet of 42 to 91 percent, depending on the definition of adherence and method of ascertainment.[30] Adherence was lowest among ethnic minorities and persons diagnosed in childhood, and rates of adherence were similar among screen-detected and symptomatic patients. Patients who do not respond to a gluten-free diet are often evaluated for concurrent lactose or other carbohydrate intolerance, pancreatic insufficiency, inflammatory bowel disease, and functional gastrointestinal disorders.[9]

Refractory celiac disease occurs in a minority of patients and is characterized by ongoing symptoms of malabsorption despite adherence to a gluten-free diet for 6 to12 months. These patients may receive treatment with corticosteroids and other immunosuppressive agents such as azathioprine, 6-mercaptopurine, or cyclosporine. Data regarding the effectiveness of these agents is limited to observational studies.[9]

Current Clinical Practice/Recommendations of Other Groups

Clinical practice guidelines recommend testing for celiac disease among persons with signs and symptoms of malabsorption as well as certain populations of asymptomatic persons at increased risk for celiac disease (**Table 1**).[26, 31-33] Reliable data on the frequency of screening for celiac disease in clinical practice is not available.[12, 24]

The complex clinical spectrum of celiac disease complicates diagnosis and management. Due to recent media attention to gluten and its potential adverse effects on health, many persons start a gluten-free diet without medical advice.[12] Some experience improvement in gastrointestinal symptoms that are attributed to celiac disease. As discussed previously, clinical improvement on a gluten-free diet is not diagnostic of celiac disease, as many other forms of gluten reaction have been described. Symptomatic improvement may also be due to a placebo effect or to other healthful changes that occur in conjunction with a modified diet.

Chapter 2. Methods

Key Questions and Analytic Framework

Using the methods developed by the USPSTF,[34] the USPSTF and AHRQ determined the scope and key questions for this review. In conjunction with USPSTF members and the AHRQ Medical Officer, investigators created an analytic framework with the key questions and the patient populations, interventions, and outcomes reviewed (**Figure**).

Key Questions

1. What is the effectiveness of screening versus 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 versus 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?

We also addressed two contextual questions requested by the USPSTF to help inform the report. Contextual questions address background areas identified by the USPSTF for informing its recommendations and are not reviewed using systematic review methodology, but rather summarize important contextual evidence.[34]

Contextual Questions

1. Among patients without overt symptoms, what is the prevalence of celiac disease in children, adolescents, and adults in the United States?
2. What is the natural history of subclinical or silent celiac disease?

Search Strategies

We searched the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews and Ovid MEDLINE (to mid-June 2016) for relevant studies and systematic reviews. Search strategies are available in **Appendix A1**. We also reviewed reference lists of relevant articles.

Study Selection

At least two reviewers independently evaluated each study to determine inclusion eligibility. We selected studies on the basis of inclusion and exclusion criteria developed for each key question (**Appendix A2**). For screening and diagnosis, the population of interest was asymptomatic adults, adolescents, or children age 3 years or older without known celiac disease who had not sought evaluation for potential celiac disease, including persons at higher risk due to family history or presence of conditions associated with celiac disease. For treatment, the population of interest was persons with screen-detected celiac disease who were asymptomatic. We included studies of mildly symptomatic patients if no studies were available in asymptomatic populations. Screening tests were serologic tests or questionnaires. We included randomized trials, cohort studies, and case-control studies performed in primary care or primary care–applicable settings of screening versus no screening, targeted versus universal screening, treatment versus no treatment, and immediate versus delayed treatment that reported morbidity (including outcomes related to nutritional deficiencies, gastrointestinal symptoms), cancer incidence, mood and anxiety, child growth outcomes, infection rates, quality of life, or mortality. For diagnostic accuracy, we included cohort and cross-sectional studies that compared screening tests against endoscopy with biopsy as the reference standard. We excluded studies that focused on intermediate outcomes such as laboratory values for nutritional or other deficiencies and studies that evaluated diagnostic accuracy using a case-control design. To summarize the diagnostic accuracy of screening tests in populations that were not asymptomatic, we included good-quality systematic reviews. The selection of literature is summarized in the literature flow diagram (**Appendix A3**). **Appendix A4** lists excluded studies with reasons for exclusion.

Data Abstraction and Quality Rating

One investigator abstracted details about each article's study design, patient population, setting, screening method, treatment regimen, analysis, followup, and results. A second investigator reviewed data abstraction for accuracy. Two investigators independently applied criteria developed by the USPSTF[34] to rate the quality of each study as good, fair, or poor (**Appendix A5**). Discrepancies were resolved through consensus.

Data Synthesis

We assessed the aggregate internal validity (quality) of the body of evidence for each key question ("good," "fair," or "poor") using methods developed by the USPSTF, based on the number, quality and size of studies, consistency of results between studies, and directness of evidence.[34] There were too few studies to perform meta-analysis.

External Review

The draft report was reviewed by content experts, USPSTF members, AHRQ Project Officers, and collaborative partners, and posted for public comment.

Response to Public Comments

The draft report was posted for public comment on the USPSTF Web site from May 3, 2016 to May 30, 2016, and few comments were received. No comments identified missing studies or errors in the evidence reviewed, resulting in no changes to the findings or conclusions of the report.

Chapter 3. Results

Key Question 1. What Is the Effectiveness of Screening Versus Not Screening for Celiac Disease in Asymptomatic Adults, Adolescents, or Children on Morbidity, Mortality, or Quality of Life?

We identified no studies on the effectiveness of screening versus no 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 Versus Universal Screening for Celiac Disease in Asymptomatic Adults, Adolescents, or Children on Morbidity, Mortality, or Quality of Life?

We identified no studies on the effectiveness of targeted screening of persons with a family history or other risk factors for celiac disease versus 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?

We identified no trials on the harms of screening versus no screening for celiac disease.

Key Question 4. What Is the Accuracy of Screening Tests for Celiac Disease?

Summary

One good-quality systematic review found that tTG antibody tests were 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 percent (95% CI, 90.3% to 94.8%) and specificity was 97.9 percent (95% CI, 96.4% to 98.8%), for a positive likelihood ratio (PLR) of 45.1 (95% CI, 25.1 to 75.5) and negative likelihood ratio (NLR) of 0.07 (95% CI, 0.05 to 0.10). EMA tests were also associated with strong likelihood ratios. Limited evidence from two studies of serologic testing in asymptomatic, high-risk children and younger adults reported lower sensitivity (57% to 71%); specificity ranged from 83 to 98 percent.

Evidence

A recent good-quality systematic review on the diagnostic accuracy of tests for celiac disease included 56 original studies and 12 prior systematic reviews (**Appendixes B1** and **B2**).[35] Sample sizes ranged from 62 to more than 12,000 subjects. Three primary studies focused on diagnostic accuracy of testing in children and/or adolescents,[36-38] six evaluated a mixed population of children and adults,[39-44] and the remainder focused on adults. One study was conducted in the United States,[45] five studies in the Middle East,[40, 42, 46-48] one in India,[49] one in Argentina,[50] and the rest in Europe.[36-39, 41, 43, 44, 51-58] Tests evaluated included tTG, EMA, DGP, and video capsule endoscopy. Only two studies reported diagnostic accuracy in asymptomatic persons (**Appendixes B3** and **B4**).[37, 40]

Overall, including studies of persons with symptoms or in whom symptom status was not described, the systematic review found high strength of evidence that the tTG IgA test was associated with high (>90%) sensitivity and specificity and the EMA IgA test was associated with high specificity, based on consistent results from prior systematic reviews and new studies. For the tTG IgA test, the pooled sensitivity, based on new studies, was 92.8 percent (95% CI, 90.3% to 94.8%) and specificity was 97.9% (95% CI, 96.4% to 98.8%), for a PLR of 45.1 (95% CI, 25.1 to 75.5) and NLR of 0.07 (95% CI, 0.05 to 0.10). For the EMA IgA test, the pooled sensitivity, based on new studies, was 73.0 percent (95% CI, 61.0% to 83.0%) and specificity was 99.0 percent (95% CI, 98.0% to 99.0%), for a PLR of 65.6 (95% CI, 35.6 to 120.8) and NLR of 0.28 (95% CI, 0.17 to 0.41). Results for the DGP IgA test indicated somewhat weaker likelihood ratios; the pooled sensitivity was 87.8 percent (95% CI, 85.6% to 89.9%) and specificity was 94.1 percent (95% CI, 92.5% to 95.5%), for a PLR of 13.3 (95% CI, 9.6 to 18.4) and NLR of 0.12 (95% CI, 0.08 to 0.18). For video capsule endoscopy, the pooled sensitivity was 89.0 percent (95% CI, 82.0% to 94.0%) and specificity was 95.0 percent (95% CI, 89.0% to 99.0%), for a PLR of 12.9 (95% CI, 2.9 to 57.6) and NLR of 0.16 (95% CI, 0.10 to 0.25).

Three studies in the systematic review compared the accuracy of tests by age group.[38, 41, 57] Sensitivity and specificity were generally similar across age groups, with the exception of one study that reported specificity of 26 percent for the DGP IgA test among those age 18 years or younger.[38] Sensitivity was somewhat lower in adults than in children, but differences were slight.

Only two studies included in the systematic review reported diagnostic accuracy in asymptomatic persons (**Appendixes B3** and **B4**).[37, 40] A small (n=62), fair-quality study of patients in Iraq with type 1 diabetes mellitus (mean age, 23 years) without symptoms or a family history of celiac disease evaluated tTG IgA, tTG IgG, EMA IgA, AGA IgA, and AGA IgG assays.[40] The prevalence of celiac disease, based on biopsy, was 11.3 percent (7/62); sensitivity ranged from 57 percent for the tTG IgG test to 71 percent for the tTG Ig A and EMA IgA tests, resulting in positive predictive values of 50.0 to 71.4 percent; specificity was similar across tests, ranging from 93 to 98 percent, for negative predictive values of 94.4 to 96.4 percent.

Another fair-quality study reported diagnostic accuracy of the combination of tTG IgA and EMA IgA tests in a subgroup of 158 asymptomatic Czech children and adolescents ages 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.[37] The prevalence of Marsh 2 or 3 small-bowel mucosal villous atrophy was 78.5 percent (124/158), with sensitivity of 67 percent and specificity of 83 percent for the combination of tTG IgA levels more than 10 times the upper limit of normal and a positive EMA IgA test. Results were not reported for the subgroup of patients with Marsh 3 biopsy findings. Sensitivity was 70 percent and specificity was 81 percent for patients with a first-degree relative with celiac disease (n=32); sensitivity was 64 percent and specificity was 93 percent for patients with type 1 diabetes mellitus (n=40).

Key Question 5. Does Treatment of Screen-Detected Celiac Disease Lead to Improved Morbidity, Mortality, or Quality of Life Compared With No Treatment?

Summary

One small (n=40), fair-quality trial of screen-detected, asymptomatic adults found that a gluten-free diet was associated with small improvements in gastrointestinal symptoms (<1 point on a 7-point scale) versus no gluten-free diet after 1 year, but there were no changes on most quality of life outcomes. No other study evaluated the effects of a gluten-free versus no gluten-free diet on clinical outcomes.

Evidence

One fair-quality trial (n=40) evaluated a gluten-free versus normal gluten–containing diet among screen-detected adults who were asymptomatic relatives of persons with celiac disease (**Appendixes B5** and **B6**).[59] Median age of participants was 42 years. Diagnosis of celiac disease was based on a positive serum EMA test. Although biopsy was performed, histopathologic findings of celiac disease were not required for study entry, and biopsy results were blinded from study researchers until completion of the trial. At baseline, the mean villous height to crypt depth ratio was 1.0 in the gluten-free diet group and 0.8 in the nongluten-free diet group; two patients in each group had a normal villous height to crypt depth (>2.0).

At 1 year, subjects on a gluten-free diet reported significant improvements in total gastrointestinal symptoms compared with those on a nongluten-free diet, based on the overall Gastrointestinal Symptoms Ratings Scale (difference in mean change, -0.4 on a 7-point 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 subscales (difference in mean change, -0.5 [95% CI, -0.9 to -0.1]), with no differences on the constipation or abdominal pain subscales. 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 on a 6-point scale [95% CI, 0.4 to 2.8]), with no differences on the depression, well-being, self-control, general health, or vitality subscales. There were no differences in any subscales of the Short-Form 36 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]). 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 percent of subjects reported adherence to the gluten-free diet, and improvements in histopathologic findings were observed in the gluten-free diet group at 1 year compared with the nongluten-free diet group.

An earlier, small (n=23) trial conducted at the same center did not meet inclusion criteria.[60] Although it randomized patients identified through EMA testing to a gluten-free or normal diet, 87 percent (20/23) of patients had moderate or severe symptoms. All patients had nondiagnostic (Marsh 1 or 2) histologic findings on small bowel biopsy. Over the course of 1 year, a gluten-free diet was associated with significantly improved subjective clinical symptom ratings, with all patients' ratings changing from severe/moderate to slight/no symptoms ($p<0.05$), compared with no changes on a nongluten-free diet.

Three small (n=14 to 32) studies evaluated effects of a gluten-free diet in asymptomatic adults with celiac disease but did not meet inclusion criteria because they did not have a nongluten-free diet control group.[61-63] Each study evaluated effects before initiation of a gluten-free diet and at 1 to 2 years. Following initiation of a gluten-free diet, one study found worse perceived health and more concern about health,[62] one study found no differences in measures of quality or life or general health,[61] and one study found small improvements in gastrointestinal symptoms but no differences in quality of life.[63]

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?

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

Key Question 7. What Are the Harms Associated With Treatment of Celiac Disease?

The trial of a gluten-free diet by Kurppa and colleagues (included for key question 5) reported no withdrawals "as a result of major symptoms or complications."[59] We identified no other study on harms of gluten-free versus nongluten-free diet in persons with screen-detected celiac disease.

Contextual Question 1. Among Patients Without Overt Symptoms, What Is the Prevalence of Celiac Disease in Children, Adolescents, and Adults in the United States?

Reliable data regarding the prevalence of subclinical and silent celiac disease in the United States are not available. Most prevalence studies of the general population were not designed to determine whether participants had symptoms potentially attributable to celiac disease or whether they were truly asymptomatic. In a large (n=7,798) NHANES study of persons age 6 years or older, the prevalence of celiac disease, as defined by a positive tTG IgA and EMA IgA test, was 0.71 percent among the general population, 0.76 percent among those age 20 years or older, 0.62 percent among women, and 1.01 percent among non-Hispanic whites.[4] Study participants were asked whether they had previously been diagnosed with celiac disease and whether they were on a gluten-free diet but were not interviewed regarding symptoms that could be attributed to celiac disease. Other studies of the general adult U.S. population found a celiac disease prevalence of 0.2 to 0.9 percent, based on positive serologic tests, specifically initial tTG antibody tests followed by EMA testing.[3, 5, 64] None of these studies reported whether participants had symptoms that could be caused by celiac disease. Some studies from Europe reported the proportion of patients with celiac disease who were asymptomatic. In an Italian retrospective study of 549 patients with celiac disease diagnosed by intestinal biopsy, 45.7 percent presented with classical celiac disease and 6.6 percent were asymptomatic.[19] Another Italian study found that of 770 patients with celiac disease, 79 percent presented with classical celiac disease and 21 percent presented with atypical or silent celiac disease.[65]

Presumably, many cases of celiac disease detected by screening would be subclinical or silent. However, a limitation of many studies is that diagnosis of celiac disease was based on positive results on combinations of serologic tests without histologic confirmation. However, serologic tests are associated with a small proportion of false positives in symptomatic persons. At a given diagnostic accuracy, the positive predictive value of serologic tests will be lower in populations with a lower prevalence of celiac disease.[16, 24]

Even when intestinal biopsy is performed, distinguishing between persons with false-positive serologic findings and persons with subclinical celiac disease can be a challenge, because biopsy findings may be subtle or absent due to patchy disease or inadequate sampling.[16] Most studies reported high concordance between positive serology and intestinal biopsy. However, in a study of 1,461 Estonians ages 15 to 95 years who were screened for celiac disease with AGA IgA testing, 3.5 percent (52 persons) had positive serology, but none were symptomatic or had biopsy results consistent with celiac disease.[66] Among 20 screen-detected adults in Northern Ireland with positive celiac disease serology who agreed to have intestinal biopsy, only three had villous atrophy. Of these, one was asymptomatic and two later endorsed symptoms attributed to celiac disease.[67]

Contextual Question 2. What Is the Natural History of Subclinical or Silent Celiac Disease?

Data regarding the proportion of persons with silent or subclinical celiac disease who later develop symptomatic celiac disease are limited. In a study of stored sera from young adults at Warren Air Force Base collected from 1948 to 1954, none of the 14 subjects with undiagnosed celiac disease, based on serologic tests, received a clinical diagnosis of celiac disease within 45 years of followup.[5] A study of adults in Maryland based on 3,511 matched samples of stored sera from 1974 and 1989 found that among 18 cases diagnosed with celiac disease, based on positive EMA IgA and positive/borderline results for tTG IgA, two persons received a clinical diagnosis of celiac disease at a mean followup of 31.1 years.[64] In a study of 16,847 adults age 50 years or older in Minnesota, 129 were found to have undiagnosed celiac disease, based on positive tTG IgA and EMA IgA tests.[3] During a median followup of 10.3 years, 20 persons were clinically diagnosed with celiac disease. A study of 3,654 Finnish children without known celiac disease found that 1.5 percent (56 children) had positive tTG IgA and EMA IgA or IgG tests. Over 7 years of followup, 37 (about 1%) were diagnosed with celiac disease on the basis of biopsy, of which 10 remained clinically silent.[68] A Dutch study of children ages 2 to 4 years diagnosed with celiac disease based on EMA antibodies and confirmatory biopsy through a screening program found that five of 12 asymptomatic children who did not initiate a gluten-free diet remained asymptomatic after 10 years of followup.[69] The other seven children switched to a gluten-free diet due to the development of symptoms; symptoms resolved after initiation of the diet. Another study found that among children (mean age, 29 months) with potential celiac disease (serology positive/Marsh 0–1 histology), 86 percent (18/21) who continued a gluten-containing diet become antibody negative, 9 percent (2/21) had fluctuating antibodies, and 5 percent (1/21) developed overt celiac disease.[70]

Evidence is conflicting whether persons diagnosed with subclinical or silent celiac disease experience the same mortality risk as the general population.[3, 5, 20, 67, 71-74] The Warren Air Force Base study discussed above found that all-cause mortality was higher among persons with undiagnosed celiac disease (based on positive serology) after 45 years of followup than among seronegative controls within the same cohort.[5] However, symptom status of persons with undiagnosed celiac disease was not reported. In a study of stored sera from German adults collected from 1989 to 1990, positive celiac disease serology was associated with increased risk of all-cause mortality compared with age- and sex-matched controls.[71] Participants were asked about their general self-rated health status, but as in the other study, the prevalence of symptoms attributable to celiac disease was not reported.

A meta-analysis of observational studies reported somewhat conflicting results regarding effects of celiac disease diagnosed by serologic testing and association with increased risk of all-cause mortality and cancer compared with seronegative age- and sex-matched controls.[20] In three studies, screen-detected celiac disease (diagnosed by serologic tests alone, symptoms not reported) was not associated with increased risk of all-cause or cancer mortality compared with age- and sex-matched controls.[3, 72, 73] However, a fourth study found that latent celiac disease (positive serology and normal mucosa) was associated with an estimated excess mortality of 1.7 deaths per 1,000 person-years compared with age- and sex-matched controls in the general

population (hazard ratio, 1.35 [95% CI, 1.14 to 1.58]).[74] Symptom status was not reported, but the authors noted that clinical suspicion for celiac disease was the only major indication for small intestinal biopsy in Sweden, suggesting that persons may have been symptomatic.[74] In another study of screen-detected celiac disease among adults in Northern Ireland, positive serologic tests for celiac disease were not associated with excess mortality risk compared with age-specific mortality in the general population.[67]

Some data suggest that subclinical or silent celiac disease is associated with lower risk of developing celiac disease complications than symptomatic disease (**Table 2**). An Italian retrospective study of 549 patients with celiac disease diagnosed by intestinal biopsy found that the complication rate among patients on a gluten-free diet (mean duration, 7 years [range, 1 to 15 years]) was 5.58 percent in those with classical celiac disease (n=251) and 1.53 percent in those with subclinical celiac disease (n=262, defined as the presence of gluten-sensitive enteropathy on biopsy with extraintestinal but no gastrointestinal symptoms).[19] Complications included gastrointestinal adenocarcinoma, Sjögren's syndrome, jejunal enteropathy-associated T-cell lymphoma, myocardial infarction, sclerosing cholangitis, herpetiform dermatitis, gastric mucosa-associated lymphoid tissue lymphoma, ulcerative jejunitis, severe nonalcoholic steatohepatitis, recurrent abortion, and autoimmune thrombocytopenia. There was no statistical difference between the mean age of the two groups developing complications. No patient with silent disease (gluten-sensitive enteropathy on biopsy without symptoms) experienced complications. Another Italian study of 770 patients diagnosed with celiac disease (histologic confirmation) evaluated presentation patterns of patients who developed complicated versus noncomplicated celiac disease ($p<0.001$).[65] Six patients with classic malabsorption symptoms at presentation developed complications compared with no patients with atypical and subclinical celiac disease over a mean of 5 years ($p<0.001$). Complications included enteropathy-associated T-cell lymphoma, small bowel carcinoma, and refractory celiac disease.

Chapter 4. Discussion

Summary of Review Findings

Table 3 summarizes the evidence reviewed for this update. We identified no studies of screening versus no screening for celiac disease in the target populations for this review (adults, adolescents, and children age 3 years or older). Although serologic tests for celiac disease used in screening appear to be highly accurate, almost all studies on diagnostic accuracy evaluated populations with symptoms of celiac disease or whose symptom status was not reported. Two studies that specifically evaluated 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.[37, 40]

Only one randomized trial evaluated the effectiveness of gluten-free versus no gluten-free diet in asymptomatic persons with screen-detected celiac disease.[59] It found that initiation of a gluten-free diet in screen-detected, asymptomatic adults was associated with improved gastrointestinal symptoms, though effects were relatively small (<1 point on a 7-point scale). 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, though most patients had some degree of villous atrophy at baseline. Nonetheless, it is possible that this trial could have underestimated benefits of treatment for histologic-proven celiac disease. Three small studies on effects of a gluten-free diet in persons with asymptomatic celiac disease were excluded because they did not include a gluten-containing diet control group.[61-63] There were no clear effects on quality of life, though one study[62] found increased worry about health following initiation of a gluten-free diet and one study[63] reported small improvements in gastrointestinal symptoms.

No study compared the effectiveness of targeted versus universal screening or evaluated effects of immediate initiation of a gluten-free diet versus delaying until the development of symptoms in asymptomatic persons diagnosed with celiac disease.

Limitations

The major limitation of this review is the lack of evidence to address the key questions. There were no studies on screening versus no screening, only two studies on diagnostic accuracy of serologic testing in asymptomatic populations, and only one trial of treatment in asymptomatic, screen-detected persons with celiac disease. 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 we could not formally assess for publication bias. We restricted inclusion to English-language articles but found no non-English–language articles on benefits or harms of screening or treatment that appeared to meet inclusion criteria. Although some non-English–language articles assessed diagnostic accuracy, none were clearly conducted in asymptomatic populations.

Emerging Issues/Next Steps

An emerging issue is the development and uptake of methods for diagnosing celiac disease that do not require histologic confirmation. The proportion 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 clinical practice guideline recommendations for histologic confirmation.

A related issue is how to classify and manage persons with positive serologic findings but negative or nondiagnostic findings on biopsy. The likelihood that such patients will go on to develop overt celiac disease requires further investigation, and has important implications for management.

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 versus no notification or initiation of a gluten-free diet was terminated.[75] We were unable to determine reasons for study termination.

Although there continues to be research on pharmacologic treatments for celiac disease,[76-79] such treatments are considered an adjunct to a gluten-free diet, which remains the mainstay of therapy.

Relevance for Priority Populations

In the United States, celiac disease is uncommon among racial/ethnic minorities, although it does occur. In an NHANES study, the prevalence of tTG IgA test results were 0.8 percent (27/3,430) among non-Hispanic whites, 0.07 percent (1/1,394) among non-Hispanic blacks, 0.03 percent (1/2,519) among other Hispanics/not Mexican Americans, and 0.2 percent (1/455) among other race/ethnicity categories.[4]

The only randomized trial of treatment with a gluten-free diet among asymptomatic screen-detected persons was restricted to persons younger than age 18 years or older than age 75 years.[80] Although celiac disease is most commonly diagnosed between ages 40 and 60 years,[13, 14] it can affect adolescents and children as well as older adults.[81, 82]

Future Research

Additional research is needed to address all of the key questions addressed in this report. For screening, trials of screening versus 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 be likely to provide a higher yield of screen-detected persons than trials that screen lower- or average-risk persons, 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 versus no gluten-free diet in screen-detected persons, and the effects of immediate

initiation on diagnosis versus delayed initiation until the development of symptoms. The in-progress Celiac Disease and Diabetes-Dietary Intervention and Evaluation Trial (Celiac Disease-DIET), which involves screening for asymptomatic celiac disease in children and adults with type 1 diabetes mellitus 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 persons.[83] Ideally, future studies would be carried out long enough to determine effects 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, as celiac disease can be diagnosed in any of these age groups.

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 and/or histologic findings resolve without treatment.

Conclusions

More research is needed to understand the effectiveness of screening for and treatment of celiac disease in asymptomatic adults, adolescents, and children, and optimal screening strategies.

References

1. Dube C, Rostom A, Sy R, et al. The prevalence of celiac disease in average-risk and at-risk Western European populations: a systematic review. Gastroenterology. 2005;128(4 Suppl 1):S57-67. PMID: 15825128.
2. Fasano A, Berti I, Gerarduzzi T, et al. Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study. Arch Intern Med. 2003;163(3):286-92. PMID: 12578508.
3. Godfrey JD, Brantner TL, Brinjikji W, et al. Morbidity and mortality among older individuals with undiagnosed celiac disease. Gastroenterology. 2010;139(3):763-9. PMID: 20685275.
4. Rubio-Tapia A, Ludvigsson JF, Brantner TL, et al. The prevalence of celiac disease in the United States. Am J Gastroenterol. 2012;107(10):1538-44. PMID: 22850429.
5. Rubio-Tapia A, Kyle RA, Kaplan EL, et al. Increased prevalence and mortality in undiagnosed celiac disease. Gastroenterology. 2009;137(1):88-93. PMID: 19362553.
6. Riddle MS, Murray JA, Porter CK. The incidence and risk of celiac disease in a healthy US adult population. Am J Gastroenterol. 2012;107(8):1248-55. PMID: 22584218.
7. Ludvigsson JF, Rubio-Tapia A, van Dyke CT, et al. Increasing incidence of celiac disease in a North American population. Am J Gastroenterol. 2013;108(5):818-24. PMID: 23511460.
8. Green PH, Cellier C. Celiac disease. N Engl J Med. 2007;357(17):1731-43. PMID: 17960014.
9. Crowe SE. Celiac Disease. Ann Intern Med. 2011;154(9):2-16.
10. Vriezinga SL, Auricchio R, Bravi E, et al. Randomized feeding intervention in infants at high risk for celiac disease. N Engl J Med. 2014;371(14):1304-15. PMID: 25271603.
11. Lionetti E, Castellaneta S, Francavilla R, et al. Introduction of gluten, HLA status, and the risk of celiac disease in children. The New England journal of medicine. 2014;371(14):1295-303. PMID: CN-01012187.
12. Fasano A, Catassi C. Clinical practice. Celiac disease. N Engl J Med. 2012;367(25):2419-26. PMID: 23252527.
13. Rampertab SD, Pooran N, Brar P, et al. Trends in the presentation of celiac disease. Am J Med. 2006;119(4):355 e9-14. PMID: 16564784.
14. Green PH. The many faces of celiac disease: clinical presentation of celiac disease in the adult population. Gastroenterology. 2005;128(4 Suppl 1):S74-8. PMID: 15825130.
15. Fasano A. Clinical presentation of celiac disease in the pediatric population. Gastroenterology. 2005;128(4 Suppl 1):S68-73. PMID: 15825129.
16. Rostom A, Murray JA, Kagnoff MF. American Gastroenterological Association (AGA) Institute technical review on the diagnosis and management of celiac disease. Gastroenterology. 2006;131(6):1981-2002. PMID: 17087937.
17. Ludvigsson JF, Leffler DA, Bai JC, et al. The Oslo definitions for coeliac disease and related terms. Gut. 2013;62(1):43-52. PMID: 22345659.
18. Evans KE, Hadjivassiliou M, Sanders DS. Is it time to screen for adult coeliac disease? Eur J Gastroenterol Hepatol. 2011;23(10):833-8. PMID: 21799421.
19. Tursi A, Elisei W, Giorgetti GM, et al. Complications in celiac disease under gluten-free diet. Dig Dis Sci. 2009;54(10):2175-82. PMID: 19058000.

20. Tio M, Cox MR, Eslick GD. Meta-analysis: coeliac disease and the risk of all-cause mortality, any malignancy and lymphoid malignancy. Ailment Pharmacol Ther. 2012;35(5):540-51. PMID: 22239821.
21. Mansueto P, Seidita A, D'Alcamo A, et al. Non-celiac gluten sensitivity: literature review. J Amer Coll Nutr. 2014;33(1):39-54. PMID: 24533607.
22. Biesiekierski JR, Peters SL, Newnham ED, et al. No effects of gluten in patients with self-reported non-celiac gluten sensitivity after dietary reduction of fermentable, poorly absorbed, short-chain carbohydrates. Gastroenterology. 2013;145(2):320-8 e1-3. PMID: 23648697.
23. Murray JA. Celiac disease in patients with an affected member, type 1 diabetes, iron-deficiency, or osteoporosis? Gastroenterology. 2005;128(4 Suppl 1):S52-6. PMID: 15825127.
24. Mustalahti K, Catassi C, Reunanen A, et al. The prevalence of celiac disease in Europe: results of a centralized, international mass screening project. Ann Med. 2010;42(8):587-95. PMID: 21070098.
25. Green PHR, Stavropoulos SN, Panagi SG, et al. Characteristics of adult celiac disease in the USA: results of a national survey. Am J Gastroenterol. 2001;96(1):126-31. PMID: 11197241.
26. Rubio-Tapia A, Hill ID, Kelly CP, et al. ACG clinical guidelines: diagnosis and management of celiac disease. Am J Gastroenterol. 2013;108(5):656-76. PMID: 23609613.
27. Richey R, Howdle P, Shaw E, et al. Recognition and assessment of coeliac disease in children and adults: summary of NICE guidance. BMJ. 2009;338:1684-8. PMID: 19474030.
28. Burgin-Wolff A, Mauro B, Faruk H. Intestinal biopsy is not always required to diagnose celiac disease: a retrospective analysis of combined antibody tests. BMC Gastroenterol. 2013;13:19. PMID: 23343249.
29. U.S. Food and Drug Administration. 'Gluten-Free' Now Means What It Says. Accessed at http://www.fda.gov/forconsumers/consumerupdates/ucm363069.htm#gluten-free on August 25, 2015.
30. Hall NJ, Rubin G, Charnock A. Systematic review: adherence to a gluten-free diet in adult patients with coeliac disease. Aliment Pharmacol Ther. 2009;30(4):315-30. PMID: 19485977.
31. National Institute for Health and Care Excellence. Coeliac disease: recognition, assessment, and managment: NICE Guideline [NG20]; 2015. Accessed at www.nice.org.uk/guidance/ng20 on September 22, 2015.
32. Medical Advisory Secretariat. Clinical utility of serologic testing for celiac disease in asymptomatic patients: an evidence-based analysis. Ont Health Technol Assess Ser. 2011;11(3):1-63. PMID: 23074415.
33. Hill ID, Dirks MH, Liptak GS, et al. Guideline for the diagnosis and treatment of celiac disease in children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Ntr. 2005;40(1):1-19. PMID: 15625418.
34. U.S. Preventive Services Task Force. Procedure Manual. Accessed at http://www.uspreventiveservicestaskforce.org/Page/Name/procedure-manual on August 25, 2015.

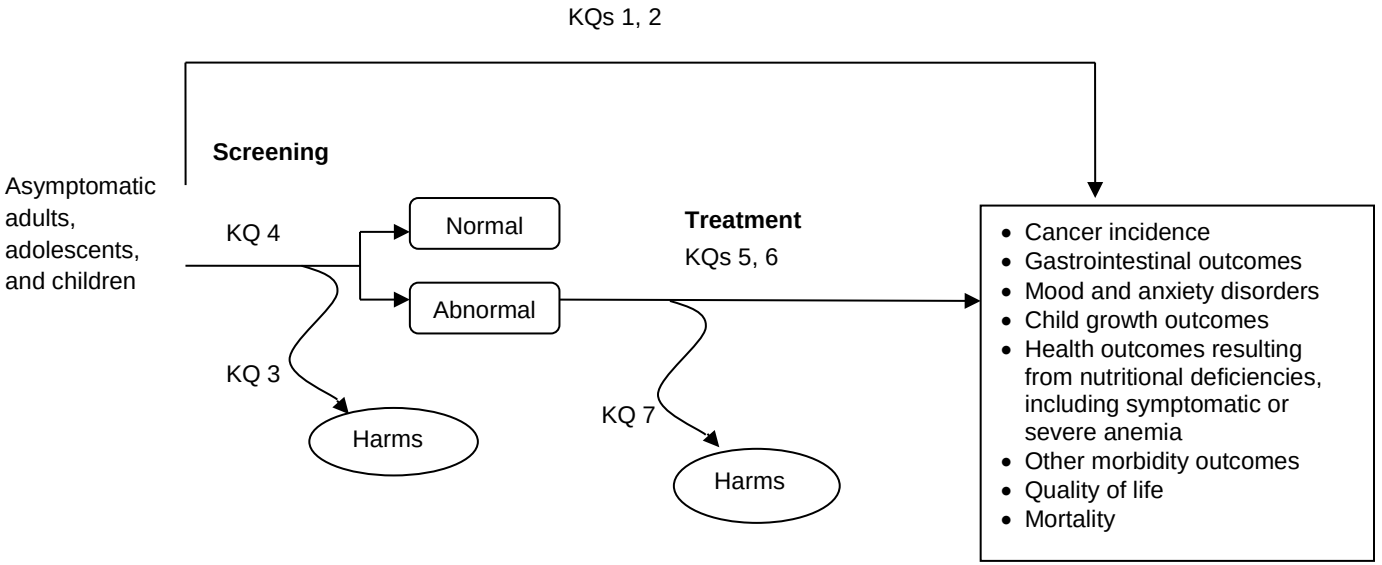
35. Maglione M, Okunogbe A, Ewing B, et al. Diagnosis of Celiac Disease. Comparative Effectiveness Review No. 162. (Prepared by the Southern California Evidence-based Practice Center under Contract No. 290-2012-00006-I.). Rockville, MD. 2016.
36. Basso D, Guariso G, Bozzato D, et al. New screening tests enrich anti-transglutaminase results and support a highly sensitive two-test based strategy for celiac disease diagnosis. Clin Chim Acta. 2011;412(17-18):1662-7. PMID: 21640087.
37. Nevoral J, Kotalova R, Hradsky O, et al. Symptom positivity is essential for omitting biopsy in children with suspected celiac disease according to the new ESPGHAN guidelines. Eur J Pediatr. 2014;173:497-502. PMID: 24233405.
38. Olen O, Gudjonsdottir AH, Browaldh L, et al. Antibodies against deamidated gliadin peptides and tissue transglutaminase for diagnosis of pediatric celiac disease. J Pediatr Gastroenterol Ntr. 2012;55(6):695-700. PMID: 22722680.
39. Dahlbom I, Korponay-Szabo IR, Kovacs JB, et al. Prediction of clinical and mucosal severity of coeliac disease and dermatitis herpetiformis by quantification of IgA/IgG serum antibodies to tissue transglutaminase. J Pediatr Gastroenterol Ntr. 2010;50(2):140-6. PMID: 19841593.
40. Mansour AA, Najeeb AA. Coeliac disease in Iraqi type 1 diabetic patients. Arab J Gastroenterol. 2011;12(2):103-5. PMID: 21684484.
41. Mozo L, Gomez J, Escanlar E, et al. Diagnostic value of anti-deamidated gliadin peptide IgG antibodies for celiac disease in children and IgA-deficient patients. J Pediatr Gastroenterol Ntr. 2012;55(1):50-5. PMID: 22197936.
42. Sakly W, Mankai A, Ghdess A, et al. Performance of anti-deamidated gliadin peptides antibodies in celiac disease diagnosis. Clin Res Hepatol Gastroenterol. 2012;36(6):598-603. PMID: 22436429.
43. Van Meensel B, Hiele M, Hoffman I, et al. Diagnostic accuracy of ten second-generation (human) tissue transglutaminase antibody assays in celiac disease. Clin Chem. 2004;50(11):2125-35. PMID: 15388634.
44. Vermeersch P, Geboes K, Marien G, et al. Serological diagnosis of celiac disease: comparative analysis of different strategies. Clin Chim Acta. 2012;413(21-22):1761-7. PMID: 22771970.
45. DeGaetani M, Tennyson CA, Lebwohl B, et al. Villous atrophy and negative celiac serology: a diagnostic and therapeutic dilemma. Am J Gastroenterol. 2013;108(5):647-53. PMID: 23644957.
46. Barada K, Habib RH, Malli A, et al. Prediction of celiac disease at endoscopy. Endoscopy. 2014;46(2):110-9. PMID: 24477366.
47. Cekin AH, Cekin Y, Sezer C. Celiac disease prevalence in patients with iron deficiency anemia. Turk J Gastroenterol. 2012;23(5):490-5. PMID: 23161292.
48. Emami MH, Karimi S, Kouhestani S. Is routine duodenal biopsy necessary for the detection of celiac disease in patients presenting with iron deficiency anemia? Int J Prev Med. 2012;3(4):273-7. PMID: 22624084.
49. Dutta AK, Chacko A, Avinash B. Suboptimal performance of IgG anti-tissue transglutaminase in the diagnosis of celiac disease in a tropical country. Dig Dis Sci. 2010;55(3):698-702. PMID: 19333755.
50. Sugai E, Hwang HJ, Vazquez H, et al. New serology assays can detect gluten sensitivity among enteropathy patients seronegative for anti-tissue transglutaminase. Clin Chem. 2010;56(4):661-5. PMID: 20022983.

51. Dahle C, Hagman A, Ignatova S, et al. Antibodies against deamidated gliadin peptides identify adult coeliac disease patients negative for antibodies against endomysium and tissue transglutaminase. Ailment Pharmacol Ther. 2010;32(2):254-60. PMID: 20456302.
52. Harrison E, Li K-K, Petchey M, et al. Selective measurement of anti-tTG antibodies in coeliac disease and IgA deficiency: an alternative pathway. Postgrad Med J. 2013;89(1047):4-7. PMID: 22872871.
53. Kaukinen K, Collin P, Mykkanen AH, et al. Celiac disease and autoimmune endocrinologic disorders. Dig Dis Sci. 1999;44(7):1428-33. PMID: 10489930.
54. Srinivas M, Basumani P, Podmore G, et al. Utility of testing patients, on presentation, for serologic features of celiac disease. Clin Gastroenterol Hepatol. 2014;12(6):946-52. PMID: 24262940.
55. Swallow K, Wild G, Sargur R, et al. Quality not quantity for transglutaminase antibody 2: the performance of an endomysial and tissue transglutaminase test in screening coeliac disease remains stable over time. Clin Exp Immunol. 2013;171(1):100-6. PMID: 23199329.
56. Vermeersch P, Coenen D, Geboes K, et al. Use of likelihood ratios improves clinical interpretation of IgA anti-tTG antibody testing for celiac disease. Clin Chim Acta. 2010;411(1-2):13-7. PMID: 19799890.
57. Vermeersch P, Geboes K, Marien G, et al. Diagnostic performance of IgG anti-deamidated gliadin peptide antibody assays is comparable to IgA anti-tTG in celiac disease. Clin Chim Acta. 2010;411(13-14):931-5. PMID: 20171961.
58. Zanini B, Magni A, Caselani F, et al. High tissue-transglutaminase antibody level predicts small intestinal villous atrophy in adult patients at high risk of celiac disease. Dig Liver Dis. 2012;44(4):280-5. PMID: 22119616.
59. Kurppa K, Paavola A, Collin P, et al. Benefits of a gluten-free diet for asymptomatic patients with serologic markers of celiac disease. Gastroenterology. 2014;147(3):610-7 e1. PMID: 24837306.
60. Kurppa K, Collin P, Viljamaa M, et al. Diagnosing mild enteropathy celiac disease: a randomized, controlled clinical study. Gastroenterology. 2009;136(3):816-23. PMID: 19111551.
61. Johnston SD, Rodgers C, Watson RG. Quality of life in screen-detected and typical coeliac disease and the effect of excluding dietary gluten. Eur J Gastroenterol Hepatol. 2004;16(12):1281-6. PMID: 15618833.
62. Ukkola A, Maki M, Kurppa K, et al. Diet improves perception of health and well-being in symptomatic, but not asymptomatic, patients with celiac disease. Clin Gastroenterol Hepatol. 2011;9(2):118-23. PMID: 21029791.
63. Vilppula A, Kaukinen K, Luostarinen L, et al. Clinical benefit of gluten-free diet in screen-detected older celiac disease patients. BMC Gastroenterol. 2011;11:136. PMID: 22176557.
64. Catassi C, Kryszak D, Bhatti B, et al. Natural history of celiac disease autoimmunity in a USA cohort followed since 1974. Ann Med. 2010;42(7):530-8. PMID: 20868314.
65. Volta U, Caio G, Stanghellini V, et al. The changing clinical profile of celiac disease: a 15-year experience (1998-2012) in an Italian referral center. BMC Gastroenterol. 2014;14(1):194. PMID: 25404189.

66. Uibo O, Uibo R, Kleimola V, et al. Serum IgA anti-gliadin antibodies in an adult population sample. High prevalence without celiac disease. Dig Dis Sci. 1993;38(11):2034-7. PMID: 8223078.
67. Johnston SD, Watson RG, McMillan SA, et al. Coeliac disease detected by screening is not silent--simply unrecognized. QJM. 1998;91(12):853-60. PMID: 10024951.
68. Maki M, Mustalahti K, Kokkonen J, et al. Prevalence of Celiac disease among children in Finland. N Engl J Med. 2003;348(25):2517-24. PMID: 12815137.
69. van Koppen EJ, Schweizer JJ, Csizmadia CG, et al. Long-term health and quality-of-life consequences of mass screening for childhood celiac disease: a 10-year follow-up study. Pediatrics. 2009;123(4):e582-8. PMID: 19336349.
70. Lionetti E, Castellaneta S, Pulvirenti A, et al. Prevalence and natural history of potential celiac disease in at-family-risk infants prospectively investigated from birth. J Pediatr. 2012;161(5):908-14.e2. PMID: 22704250.
71. Metzger M-H, Heier M, Maki M, et al. Mortality excess in individuals with elevated IgA anti-transglutaminase antibodies: the KORA/MONICA Augsburg cohort study 1989-1998. Eur J Epidemiol. 2006;21(5):359-65. PMID: 16649072.
72. Canavan C, Logan RF, Khaw KT, et al. No difference in mortality in undetected coeliac disease compared with the general population: a UK cohort study. Aliment Pharmacol Ther. 2011;34(8):1012-9. PMID: 21848796.
73. Lohi S, Maki M, Rissanen H, et al. Prognosis of unrecognized coeliac disease as regards mortality: a population-based cohort study. Ann Med. 2009;41(7):508-15. PMID: 19551537.
74. Ludvigsson JF, Montgomery SM, Ekbom A, et al. Small-intestinal histopathology and mortality risk in celiac disease. JAMA. 2009;302(11):1171-8. PMID: 19755695.
75. Leffler D, Beth Israel Deaconnes Medical Center. A prospective trial of celiac disease screening. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Accessed at https://www.clinicaltrials.gov/ct2/show/NCT01902368?term=celiac+disease&rank=19 on August 25, 2015. ClinicalTrials.gov Identifier: NCT01902368.
76. Lahdeaho ML. Safety and efficacy of ALV003 for the treatment of celiac disease. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Accessed at https://www.clinicaltrials.gov/ct2/show/NCT00959114?term=celiac+disease&rank=14 on August 25, 2015. ClinicalTrials.gov Identifier: NCT00959114.
77. Rasmussen H. A double-blind placebo-controlled study to evaluate larazotide acetate for the treatment of celiac disease. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Accessed at https://www.clinicaltrials.gov/ct2/show/NCT01396213?term=celiac+disease&rank=11 on August 25, 2015. ClinicalTrials.gov Identifier: NCT01396213.
78. Leon F. Phase IIb study to study the efficacy of AT1001 to treat celiac disease. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Accessed at https://www.clinicaltrials.gov/ct2/show/NCT00492960?term=celiac+disease&rank=24 on August 25, 2015. ClinicalTrials.gov Identifier: NCT00492960
79. Makharia G. Effect of addition of short course of prednisolone to gluten free diet in naive celiac disease patients (celiac disease). In: ClinicalTrials.gov [Internet]. Bethesda (MD):

National Library of Medicine (US). Accessed at https://www.clinicaltrials.gov/ct2/show/NCT01045837?term=celiac+disease&rank=29 on August 25, 2015. ClinicalTrials.gov Identifier: NCT01045837
80. Kurppa K, Hietikko M, Sulic AM, et al. Current status of drugs in development for celiac disease. Expert Opin Investig Drugs. 2014;23(8):1079-91. PMID: 24806736.
81. Hill I, Fasano A, Schwartz R, et al. The prevalence of celiac disease in at-risk groups of children in the United States. J Pediatr. 2000;136(1):86-90. PMID: 10636980.
82. Tai V, Crowe M, O'Keefe S. Celiac disease in older people. J Am Geriatr Soc. 2000;48(12):1690-6. PMID: 11129763.
83. Mahmud FH, De Melo EN, Noordin K, et al. The celiac disease and diabetes-dietary intervention and evaluation trial (celiac disease-DIET) protocol: a randomised controlled study to evaluate treatment of asymptomatic coeliac disease in type 1 diabetes. BMJ Open. 2015;5(5):e008097. PMID: 25968008.

Figure. Analytic Framework



Abbreviation: KQ=key question.

Table 1. Recommendations of Other Groups

Organization	Screening/Testing Recommendation for Celiac Disease
American College of Gastroenterology[26]	• Persons with signs/symptoms of malabsorption • Symptomatic persons with type 1 diabetes mellitus • Asymptomatic persons with elevated serum aminotransferase • Symptomatic and asymptomatic first-degree relatives of patients with celiac disease
National Institute for Health and Care Excellence, United Kingdom[31]	• Persons with any of the following: o Persistent unexplained abdominal or gastrointestinal symptoms o Faltering growth o Prolonged fatigue o Unexpected weight loss o Severe or persistent mouth ulcers o Unexplained iron, vitamin B12, or folate deficiency o Type 1 diabetes, at diagnosis o Autoimmune thyroid disease, at diagnosis o Irritable bowel syndrome (in adults) • First-degree relatives of persons with celiac disease • Consider serologic testing for persons with any of the following: o Metabolic bone disorder (reduced bone mineral density or osteomalacia) o Unexplained neurological symptoms (particularly peripheral neuropathy or ataxia) o Unexplained subfertility or recurrent miscarriage o Persistently raised liver enzymes with unknown cause o Dental enamel defects o Down syndrome o Turner syndrome
North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition[33]	• Asymptomatic children age ≥3 years with type 1 diabetes mellitus, autoimmune thyroiditis, Down syndrome, Turner syndrome, Williams syndrome, and selective IgA deficiency • Asymptomatic children age ≥3 years who are first-degree relatives of patients with celiac disease • Children with failure to thrive, persistent diarrhea, and other gastrointestinal symptoms • Children with dermatitis herpetiformis, dental enamel hypoplasia of permanent teeth, osteoporosis, short stature, delayed puberty, and iron-deficiency anemia resistant to oral iron
Ontario Health Technology Advisory Committee[32]	• Persons with signs/symptoms of malabsorption • Persons with unexplained iron-deficiency anemia unresponsive to iron supplementation • Persons with dermatitis herpetiformis

Abbreviation: IgA=immunoglobin A.

Table 2. Natural History of Celiac Disease

Author, year	Population Country N Age	Duration of followup	Definition of CD	Prevalence		Health outcomes	
				Classic CD	Nonclassic CD (including screen-detected)	Classic CD	Nonclassic CD (including screen-detected)
Systematic review, meta-analysis (17 studies)							
Tio, 2012[20]	Symptomatic and screen-detected CD patients U.S. and Europe N=313,827 Mean age NR	NR	Varied	NR	NR	All-cause mortality: OR, 1.24 (95% CI, 1.19-1.30) Mortality from non-Hodgkin lymphoma: OR, 2.61 (95% CI, 2.04-3.33)	All-cause mortality: OR, 1.16 (95% CI, 1.02-1.31) Mortality from non-Hodgkin lymphoma: OR, 2.55 (95% CI, 1.02-6.36)
Retrospective cohort studies with comparison groups							
Canavan, 2011[72]	Population-based sample of adults from 1990-1995 United Kingdom N=7,527 Mean age NR, range 45-76 years	Median, 16.8 years	Positive IgA EMA	NA	1.16%	NA	All-cause mortality was 9.4 deaths per 1,000 person-years (95% CI, 5.4-16.1) After adjustment for age, sex, smoking, and socioeconomic status: 0.98 (95% CI, 0.57-1.69)
Godfrey, 2010[3]	Population-based sample of adults from 1995-2001 U.S., Minnesota N=16,886 Median age 63, range 52-88 years	10.3 years	Positive tTG IgA and positive EMA IgA	NA	0.8%	NA	Hazard ratio for all-cause mortality: 0.8 (95% CI, 0.45-1.41) Hazard ratio for cancer mortality: 0.63 (95% CI, 0.16-2.48)
Johnston, 1998[67]	Population-based sample of adults, 1983 Northern Ireland N=1,204 Mean age NR	Mean, 11.6 years (range, 11.3-11.9)	Positive IgA gliadin antibody, IgA antireticulin antibody, or EMA IgA	NA	8.47%	NA	Relative risk of all-cause mortality: 0.92 (95% CI, 0.5-1.6) Relative risk of cancer mortality: 0.94 (95% CI, 0.3-2.4)
Lohi, 2009[73]	Population-based sample of adults, 1978-1980 Finland N=6,987 Mean age 51, range 30-95 years	Up to 28 years	Positive tTG IgA or EMA IgA	NA	1.1% EMA positive, 2.9% tTG positive	NA	Age- and sex-adjusted relative risk of overall mortality with positive EMA IgA: 0.78 (95% CI, 0.52-1.18) Age- and sex-adjusted relative risk of overall mortality with positive tTG IgA: 1.19 (95% CI, 0.99-1.42)

Table 2. Natural History of Celiac Disease

Author, year	Population Country N Age	Duration of followup	Definition of CD	Prevalence		Health outcomes	
				Classic CD	Nonclassic CD (including screen-detected)	Classic CD	Nonclassic CD (including screen-detected)
Ludvigsson, 2009[74]	Adults who had small intestinal biopsy with CD or latent CD Sweden N=46,121 Median age 30 (with CD) and 36 (with latent CD)	8.8 years (with CD), 6.7 years (with latent CD)	Villous atrophy on small intestinal biopsy	NR	NR	Hazard ratio for all-cause mortality in CD: 1.39 (95% CI, 1.33-1.45)	Hazard ratio for all-cause mortality in latent CD: 1.35 (95% CI, 1.14-1.58)
Metzger, 2006[71]	Population-based sample of adults from 1989-1990 Southern Germany N=4,633 Mean age men, 57 years Mean age women, 53 years	Median, 7.95 years (range, 11 days-8.9 years)	Positive tTG IgA test	NA	1.36%	NA	Age-adjusted hazard ratio for all-cause mortality: 2.53 (95% CI, 1.5-4.25) Age-adjusted hazard ratio for cancer mortality: 3.62 (95% CI, 1.67-7.81)
Rubio-Tapia, 2009[5]	Healthy adults U.S., Warren AFB N=9,133 Mean age 21 years	45 years	Positive tTG IgA or EMA IgA	NA	0.2%	NA	Hazard ratio for all-cause mortality: 3.9 (95% CI, 2.0-7.5)
Tursi, 2009[19]	CD patients on gluten-free diet enrolled 1993-2006 Italy N=549 Mean age NR	NR	Positive small bowel biopsy	45.7%	47.7% subclinical* 6.6% silent	Rate of complications: 5.6%	Rate of complications: 1.5% subclinical 0% silent
Volta, 2014[65]	Adults diagnosed with CD 1998-2012 Italy N=770 Median age 36 years	Mean, 5 years (range, 18 months-14 years)	Varied (combination of duodenal biopsy, serology, and HLA typing based on patient-specific factors)	79%	21%	Rate of complications (enteropathy-associated T-cell lymphoma, small bowel carcinoma, and refractory CD): 0.9%†	Rate of complications (enteropathy-associated T-cell lymphoma, small bowel carcinoma, and refractory CD): 0%†

*Subclinical defined by presence of gluten-sensitive enteropathy with extraintestinal symptoms and no gastrointestinal symptoms.
†Difference between groups: p<0.001.

Abbreviations: AFB=Air Force Base; CD=celiac disease; CI=confidence interval; EMA=anti-endomysial antibody; HLA=human leukocyte antigen; IgA=immunoglobin A; NA=not applicable; NR=not reported; OR=odds ratio; tTG=tissue transglutaminase.

Table 3. Summary of Evidence

Included studies	Summary of findings	Consistency	Applicability	Limitations	Overall quality
Key Question 1. What is the effectiveness of screening versus not screening for celiac disease in asymptomatic adults, adolescents, or children on morbidity, mortality, or quality of life?					
No studies	-	-	-	-	-
Key Question 2. What is the effectiveness of targeted versus 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.)					
No studies	-	-	-	-	-
Key Question 3. What are the harms of screening for celiac disease?					
No studies	-	-	-	-	-
Key Question 4. What is the accuracy of screening tests for celiac disease?					
1 systematic review (of 56 studies and 12 other systematic reviews)	One good-quality systematic review found that tTG antibody tests were 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% to 94.8%) and specificity was 97.9% (95% CI, 96.4% to 98.8%), for a positive likelihood ratio of 45.1 (95% CI, 25.1 to 75.5) and negative likelihood ratio of 0.07 (95% CI, 0.05 to 0.10). EMA antibody tests were also associated with strong likelihood ratios.	Consistent	Moderate	Only 2 studies are of asymptomatic persons	Fair
2 studies (n=220) conducted in asymptomatic persons	Limited evidence from 2 studies of serologic testing in asymptomatic, high-risk children and younger adults reported lower sensitivity (57% to 71%); specificity ranged from 83% to 98%.	-	High Non-U.S. setting	Imprecision	Poor
Key Question 5. Does treatment of screen-detected celiac disease lead to improved morbidity, mortality, or quality of life compared with no treatment?					
1 trial (n=40 randomized from screening pool of 3,031)	One small (n=40), fair-quality trial of screen-detected, asymptomatic adults found that a gluten-free diet was associated with small improvements in gastrointestinal symptoms (<1 point on a 7-point scale) versus no gluten-free diet after 1 year, but there were no changes on most quality of life outcomes.	-	High Non-U.S. setting	Imprecision	Poor
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 studies	-	-	-	-	-
Key Question 7. What are the harms associated with treatment of celiac disease?					
1 trial (n=40 randomized from screening pool of 3,031)	The trial included for key question 5 reported no withdrawals "as a result of major symptoms or complications." We identified no other study on harms of gluten-free vs. nongluten-free diet in persons with screen-detected celiac disease.	-	High Non-U.S. setting	Imprecision	Poor

Abbreviations: CI=confidence interval; EMA=endomysial antibody; tTG=tissue transglutaminase.

Appendix A1. Search Strategies

Screening Effectiveness and Harms

Database: Ovid MEDLINE and Ovid OLDMEDLINE

1 Celiac Disease/
2 (celiac adj1 (disease or sprue)).mp.
3 1 or 2
4 Mass Screening/
5 3 and 4
6 screening.ti,ab.
7 3 and 6
8 5 or 7
9 limit 8 to humans
10 limit 9 to English language
11 limit 9 to abstracts
12 10 or 11
13 limit 12 to (clinical trial, all or comparative study or controlled clinical trial or randomized controlled trial)
14 12 and (random$ or control$ or cohort).mp.
15 13 or 14
16 meta-analysis.mp. or exp Meta-Analysis/
17 (cochrane or medline).tw.
18 search$.tw.
19 16 or 17 or 18
20 "Review Literature as Topic"/ or systematic review.mp.
21 19 or 20
22 12 and 21
23 limit 12 to (meta analysis or systematic reviews)
24 limit 12 to evidence based medicine reviews
25 or/22-24
26 15 or 25

Database: EBM Reviews - Cochrane Central Register of Controlled Trials

1 Celiac Disease/
2 (celiac adj1 (disease or sprue)).mp.
3 1 or 2
4 Mass Screening/
5 3 and 4
6 screening.ti,ab.
7 3 and 6
8 5 or 7
9 limit 8 to English language

Diagnostic Accuracy

Database: Ovid MEDLINE and Ovid OLDMEDLINE

1 Celiac Disease/
2 (celiac adj1 (disease or sprue)).mp.
3 1 or 2
4 Immunoglobulin A/
5 Transglutaminases/
6 (IgA or TTG).mp.
7 or/4-6
8 3 and 7
9 8 and screen$.mp.
10 "Sensitivity and Specificity"/
11 (specificity or accurac$ or "predictive value").tw.

12 (sensitiv$ or diagnostic).mp.
13 or/10-12
14 3 and 13
15 14 and screen$.mp.
16 9 or 15
17 limit 16 to English language
18 limit 16 to abstracts
19 17 or 18
20 limit 19 to humans

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
1 Celiac Disease/
2 (celiac adj1 (disease or sprue)).mp.
3 1 or 2
4 Immunoglobulin A/
5 Transglutaminases/
6 (IgA or TTG).mp.
7 or/4-6
8 3 and 7
9 8 and screen$.mp.
10 "Sensitivity and Specificity"/
11 (specificity or accurac$ or "predictive value").tw.
12 (sensitiv$ or diagnostic).mp.
13 or/10-12 (
14 3 and 13
15 14 and screen$.mp.
16 9 or 15
17 limit 16 to english language
18 limit 16 to abstracts
19 17 or 18

Treatment Effectiveness and Harms

Database: Ovid MEDLINE and Ovid OLDMEDLINE
1 Celiac Disease/dh, dt, pc, th [Diet Therapy, Drug Therapy, Prevention & Control, Therapy]
2 (celiac adj1 (disease or sprue)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
3 2 and (dh or dt or pc or th).fs.
4 1 or 3
5 Diet, Gluten-Free/
6 Celiac Disease/
7 5 and 6
8 4 or 7
9 limit 8 to (clinical trial or comparative study or controlled clinical trial or randomized controlled trial)
10 8 and (random$ or control$ or cohort).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
11 9 or 10
12 limit 8 to (meta analysis or systematic reviews)
13 limit 8 to evidence based medicine reviews
14 meta-analysis.mp. or exp Meta-Analysis/
15 (cochrane or medline).tw.
16 search$.tw.
17 14 or 15 or 16

18 "Review Literature as Topic"/ or systematic review.mp.
19 17 or 18
20 8 and 19
21 11 or 12 or 13 or 20
22 limit 21 to English language
23 limit 21 to abstracts
24 22 or 23
25 limit 24 to humans

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
1 Celiac Disease/
2 (celiac adj1 (disease or sprue)).mp.
3 Diet, Gluten-Free/
4 1 or 2 or 3

Systematic Reviews (all Key Questions)

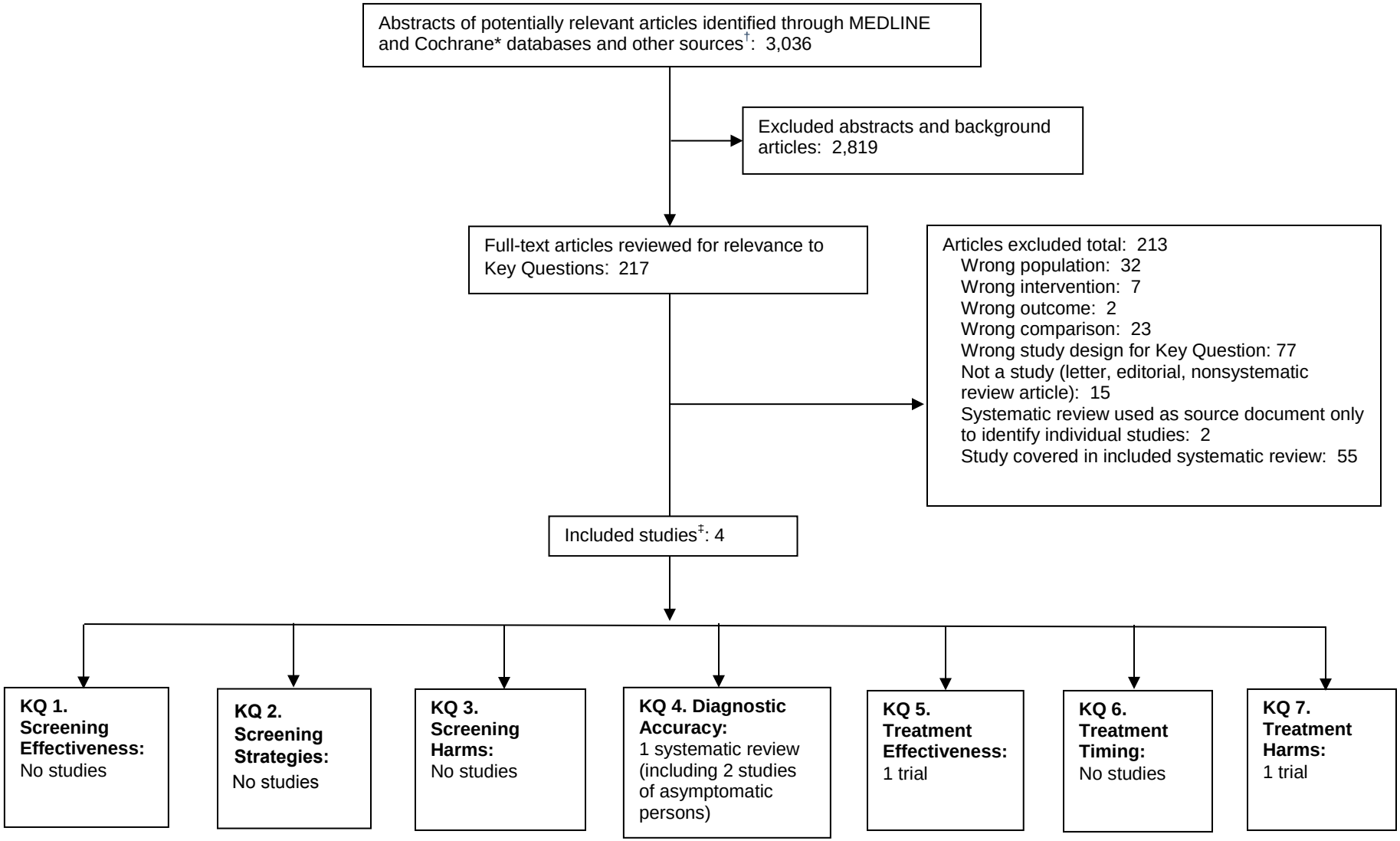
Databases: EBM Reviews - Cochrane Database of Systematic Reviews, EBM Reviews - ACP Journal Club, EBM Reviews - Database of Abstracts of Reviews of Effects, EBM Reviews - Cochrane Central Register of Controlled Trials, EBM Reviews - Cochrane Methodology Register, EBM Reviews - Health Technology Assessment, EBM Reviews - NHS Economic Evaluation Database
1 (celiac or coeliac).ti.
2 1 and gluten.mp.

Appendix A2. Inclusion and Exclusion Criteria

	Include	Exclude
Populations	**KQs 1–3:** Asymptomatic adults, adolescents, or children age ≥3 years without known celiac disease who have not sought evaluation for potential celiac disease (some "asymptomatic" individuals may have mild, nonspecific symptoms); studies of asymptomatic patients at higher risk (including patients with type 1 diabetes) **KQ 4:** Asymptomatic adults, adolescents, or children age ≥3 years without known celiac disease; studies of asymptomatic patients at higher risk (including patients with type 1 diabetes) **KQs 5–7:** Patients with screen-detected celiac disease (if evidence in such patients is unavailable or very limited, patients with mild celiac disease will be included); studies of asymptomatic patients at higher risk (including patients with type 1 diabetes)	**KQs 1–3:** Symptomatic persons seeking evaluation for potential celiac disease
Interventions	**KQs 1, 2:** Serologic screening (tTG IgA or other commonly used tests) **KQ 3:** Serologic screening (tTG IgA or other commonly used tests); diagnostic testing **KQ 4:** Serologic screening (tTG IgA or other commonly used tests); questionnaires **KQs 5–7:** Gluten-free diet	**KQ 4:** Screening with biopsy only in patients with positive serology
Comparators	**KQ 1:** Screening vs. no screening **KQ 2:** Targeted vs. universal screening **KQ 4:** Endoscopy with biopsy **KQ 5:** Screen-detected treatment vs. no treatment **KQ 6:** Screen-detected celiac disease vs. disease detected after clinical diagnosis	
Outcomes	**KQs 1, 2, 5, 6:** Morbidity (including outcomes related to nutritional deficiencies, such as symptomatic or severe anemia [i.e., requiring treatment]), gastrointestinal outcomes (e.g., diarrhea, cramping, bloating), cancer incidence, mood and anxiety disorders, child growth outcomes, infection rates, and quality of life; mortality **KQ 3:** Labeling, complications/harms from workup/biopsy, and overdiagnosis **KQ 4:** Sensitivity, specificity, positive and negative predictive values, area under the receiver operating curve, and other measures of diagnostic test accuracy **KQ 7:** Any harms of treatment	**KQs 1, 2, 5, 6:** Laboratory values for nutritional or other deficiencies
Settings	**KQs 1–3:** Primary care	**KQs 1–3:** Specialty clinics
Study designs	**KQs 1–3, 7:** Randomized, controlled trials; controlled observational studies; systematic reviews **KQ 4:** Studies evaluating diagnostic accuracy of serologic screening or questionnaires compared with intestinal biopsy; systematic reviews **KQs 5, 6:** Randomized, controlled trials; systematic reviews	**KQ 4:** Case-control studies

Abbreviations: IgA=immunoglobulin A; KQ=key question; tTG= tissue transglutaminase.

Appendix A3. Literature Flow Diagram



*Cochrane databases include the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews.
†Other sources include prior reports, reference lists of relevant articles, and systematic reviews

Appendix A4. Excluded Studies List

Arguelles-Grande C, Tennyson CA, Lewis SK, et al. Variability in small bowel histopathology reporting between different pathology practice settings: impact on the diagnosis of coeliac disease. J Clin Pathol. 2012;65(3):242-7. Excluded: Individual study in included systematic review.

Atay O, Mahajan L, Kay M, et al. Risk of capsule endoscope retention in pediatric patients: a large single-center experience and review of the literature. J Pediatr Gastroenterol Ntr. 2009;49(2):196-201. Excluded: Individual study in included systematic review.

Barada K, Habib RH, Malli A, et al. Prediction of celiac disease at endoscopy. Endoscopy. 2014;46(2):110-9. Excluded: Individual study in included systematic review.

Basso D, Guariso G, Bozzato D, et al. New screening tests enrich anti-transglutaminase results and support a highly sensitive two-test based strategy for celiac disease diagnosis. Clin Chim Acta. 2011;412(17-18):1662-7. Excluded: Individual study in included systematic review.

Bonamico M, Mariani P, Thanasi E, et al. Patchy villous atrophy of the duodenum in childhood celiac disease. J Pediatr Gastroenterol Nutr. 2004;38(2):204-7. Excluded: Individual study in included systematic review.

Bonamico M, Thanasi E, Mariani P, et al. Duodenal bulb biopsies in celiac disease: a multicenter study. J Pediatr Gastroenterol Nutr. 2008;47(5):618-22. Excluded: Individual study in included systematic review.

Bruins MJ. The clinical response to gluten challenge: a review of the literature. Nutrients. 2013;5(11):4614-41. Excluded: Individual study in included systematic review.

Caruso R, Marafini I, Del Vecchio Blanco G, et al. Sampling of proximal and distal duodenal biopsies in the diagnosis and monitoring of celiac disease. Dig Liver Dis. 2014;46(4):323-9. Excluded: Individual study in included systematic review.

Cekin AH, Cekin Y, Sezer C. Celiac disease prevalence in patients with iron deficiency anemia. Turk J Gastroenterol. 2012;23(5):490-5. Excluded: Individual study in included systematic review.

Cooper SJ, Lovatt TJ. Highs and lows of coeliac screening. Br J Biomed Sci. 2009;66(2):79-84. Excluded: Wrong study design for Key Question.

Dahlbom I, Korponay-Szabo IR, Kovacs JB, et al. Prediction of clinical and mucosal severity of coeliac disease and dermatitis herpetiformis by quantification of IgA/IgG serum antibodies to tissue transglutaminase. J Pediatr Gastroenterol Ntr. 2010;50(2):140-6. Excluded: Individual study in included systematic review.

Dahle C, Hagman A, Ignatova S, et al. Antibodies against deamidated gliadin peptides identify adult coeliac disease patients negative for antibodies against endomysium and tissue transglutaminase. Ailment Pharmacol Ther. 2010;32(2):254-60. Excluded: Individual study in included systematic review.

DeGaetani M, Tennyson CA, Lebwohl B, et al. Villous atrophy and negative celiac serology: a diagnostic and therapeutic dilemma. Am J Gastroenterol. 2013;108(5):647-53. Excluded: Individual study in included systematic review.

Dickey W, McMillan SA, McCrum EE, et al. Association between serum levels of total IgA and IgA class endomysial and antigliadin antibodies: implications for coeliac disease screening. Eur J Gastroenterol Hepatol. 1997;9(6):559-62. Excluded: Wrong study design for Key Question.

Dieterich W, Laag E, Schopper H, et al. Autoantibodies to tissue transglutaminase as predictors of celiac disease. Gastroenterology. 1998;115(6):1317-21. Excluded: Wrong population.

Diosdado B, Wapenaar MC, Franke L, et al. A microarray screen for novel candidate genes in coeliac disease pathogenesis. Gut. 2004;53(7):944-51. Excluded: Wrong intervention.

Dogan Y, Yildirmaz S, Ozercan IH. Prevalence of celiac disease among first-degree relatives of patients with celiac disease. J Pediatr Gastroenterol Nutr. 2012;55(2):205-8. Excluded: Wrong study design for Key Question.

Dutta AK, Chacko A, Avinash B. Suboptimal performance of IgG anti-tissue transglutaminase in the diagnosis of celiac disease in a tropical country. Dig Dis Sci. 2010;55(3):698-702. Excluded: Individual study in included systematic review.

Edlinger-Horvat C, Fidler D, Huber W-D, et al. Serological screening for undiagnosed coeliac disease in male adolescents in lower Austria: a population based study. Eur J Pediatr. 2005;164(1):52-3. Excluded: Wrong study design for Key Question.

El-Matary W, Huynh H, Vandermeer B. Diagnostic characteristics of given video capsule endoscopy in diagnosis of celiac disease: a meta-analysis. J Laparoendosc Adv Surg Tech A. 2009;Part A. 19(6):815-20. Excluded: Individual study in included systematic review.

Emami MH, Karimi S, Kouhestani S. Is routine duodenal biopsy necessary for the detection of celiac disease in patients presenting with iron deficiency anemia? Int J Prev Med. 2012;3(4):273-7. Excluded: Individual study in included systematic review.

Ensari A, Marsh MN, Morgan S, et al. Diagnosing coeliac disease by rectal gluten challenge: a prospective study based on immunopathology, computerized image analysis and logistic regression analysis. Clin Sci (Colch). 2001;101(2):199-207. Excluded: Wrong population.

Appendix A4. Excluded Studies List

Esteve M, Rosinach M, Fernandez-Banares F, et al. Spectrum of gluten-sensitive enteropathy in first-degree relatives of patients with coeliac disease: clinical relevance of lymphocytic enteritis. Gut. 2006;55(12):1739-45. Excluded: Wrong study design for Key Question.

Evans KE, Aziz I, Cross SS, et al. A prospective study of duodenal bulb biopsy in newly diagnosed and established adult celiac disease. Am J Gastroenterol. 2011;106(10):1837-742. Excluded: Individual study in included systematic review.

Farre C, Humbert P, Vilar P, et al. Serological markers and HLA-DQ2 haplotype among first-degree relatives of celiac patients. Catalonian Coeliac Disease Study Group. Digest Dis Sci. 1999;44(11):2344-9. Excluded: Wrong study design for Key Question.

Farrell RJ, Kelly CP. Diagnosis of celiac sprue. Am J Gastroenterol. 2001;96(12):3237-46. Excluded: Not a study (letter, editorial, non-systematic review article, no original data).

Fasano A, Berti I, Gerarduzzi T, et al. Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study. Arch Intern Med. 2003;163(3):286-92. Excluded: Wrong study design for Key Question.

Ferre-Lopez S, Ribes-Koninckx C, Genzor C, et al. Immunochromatographic sticks for tissue transglutaminase and antigliadin antibody screening in celiac disease. Clin Gastroenterol Hepatol. 2004;2(6):480-4. Excluded: Wrong study design for Key Question.

Ferretti J, Mazure R, Tanoue P, et al. Analysis of the structure and strength of bones in celiac disease patients. Am J Gastroenterol. 2003;98(2):382-90. Excluded: Wrong study design for Key Question.

Fiore CE, Pennisi P, Ferro G, et al. Altered osteoprotegerin/RANKL ratio and low bone mineral density in celiac patients on long-term treatment with gluten-free diet. Horm Metab Res. 2006;38(6):417-22. Excluded: Wrong comparator.

Ford AC, Chey WD, Talley NJ, et al. Yield of diagnostic tests for celiac disease in individuals with symptoms suggestive of irritable bowel syndrome: systematic review and meta-analysis. Arch Intern Med. 2009;169(7):651-8. Excluded: Individual study in included systematic review.

Freitag T, Schuppan D. Screening for coeliac disease antigen source and performance of the anti-tissue transglutaminase ELISA. Dig Liver Dis. 2004;36(10):658-60. Excluded: Not a study (letter, editorial, non-systematic review article, no original data).

Friis SU, Gudmand-Hoyer E. Screening for coeliac disease in adults by simultaneous determination of IgA and IgG gliadin antibodies. Scand J Gastroenterol. 1986;21(9):1058-62. Excluded: Wrong study design for Key Question.

Galli G, Esposito G, Lahner E, et al. Histological recovery and gluten-free diet adherence: A prospective 1-year follow-up study of adult patients with coeliac disease. Aliment Pharmacol Ther. 2014;40(6):639-47. Excluded: Wrong study design for Key Question.

Garrote JA, Sorell L, Alfonso P, et al. A novel visual immunoassay for coeliac disease screening. Eur J Clin Invest. 1999;29(8):697-9. Excluded: Wrong population.

Gheita TA, Fawzy SM, Nour El-Din AM, et al. Asymptomatic celiac sprue in juvenile rheumatic diseases children. Int J Rheum Dis. 2012;15(2):220-6. Excluded: Wrong population.

Ghozzi M, Sakly W, Mankai A, et al. Screening for celiac disease, by endomysial antibodies, in patients with unexplained articular manifestations. Rheumatol Int. 2014;34(5):637-42. Excluded: Wrong comparator.

Giersiepen K, Lelgemann M, Stuhldreher N, et al. Accuracy of diagnostic antibody tests for coeliac disease in children: summary of an evidence report. J Pediatr Gastroenterol Ntr. 2012;54(2):229-41. Excluded: Individual study in included systematic review.

Gillett HR, Freeman HJ. Comparison of IgA endomysium antibody and IgA tissue transglutaminase antibody in celiac disease. Can J Gastroenterol. 2000;14(8):668-71. Excluded: Wrong population.

Giordano L, Valotti M, Bosetti A, et al. Celiac disease-related antibodies in Italian children with epilepsy. Pediatr Neurol. 2009;41(1):34-6. Excluded: Wrong population.

Goh VL, Estrada DE, Lerer T, et al. Effect of gluten-free diet on growth and glycemic control in children with type 1 diabetes and asymptomatic celiac disease. J Pediatr Endocrinol. 2010;23(11):1169-73. Excluded: Wrong study design for Key Question.

Gomez JC, Selvaggio G, Pizarro B, et al. Value of a screening algorithm for celiac disease using tissue transglutaminase antibodies as first level in a population-based study. Am J Gastroenterol. 2002;97(11):2785-90. Excluded: Wrong comparator.

Gomez V, Cheesman AR, Heckman MG, et al. Safety of capsule endoscopy in the octogenarian as compared with younger patients. Gastrointest Endosc. 2013;78(5):744-9. Excluded: Individual study in included systematic review.

Gonczi J, Skerritt JH, Mitchell JD. A reliable screening test for coeliac disease: enzyme-linked immunosorbent assay to detect anti-gliadin antibodies in serum. Aust N Z J Med. 1991;21(5):723-31. Excluded: Wrong population.

Gonzalez D, Mazure R, Mautalen C, et al. Body composition and bone mineral density in untreated and treated patients with celiac disease. Bone. 1995;16(2):231-4. Excluded: Wrong study design for Key Question.

Appendix A4. Excluded Studies List

Grainge MJ, West J, Solaymani-Dodaran M, et al. The long-term risk of malignancy following a diagnosis of coeliac disease or dermatitis herpetiformis: a cohort study. Aliment Pharmacol Ther. 2012;35(6):730-9. Excluded: Wrong study design for Key Question.

Greco L, Troncone R, De Vizia B, et al. Discriminant analysis for the diagnosis of childhood celiac disease. J Pediatr Gastroenterol Nutr. 1987;6(4):538-42. Excluded: Wrong study design for Key Question.

Green PH. Mortality in celiac disease, intestinal inflammation, and gluten sensitivity. JAMA. 2009;302(11):1225-6. Excluded: Not a study (letter, editorial, non-systematic review article, no original data).

Grodzinsky E, Hed J, Lieden G, et al. Presence of IgA and IgG antigliadin antibodies in healthy adults as measured by micro-ELISA. Effect of various cutoff levels on specificity and sensitivity when diagnosing coeliac disease. Int Arch Allergy Appl Immunol. 1990;92(2):119-23. Excluded: Wrong study design for Key Question.

Grodzinsky E, Hed J, Skogh T. IgA antiendomysium antibodies have a high positive predictive value for celiac disease in asymptomatic patients. Allergy. 1994;49(8):593-7. Excluded: Wrong study design for Key Question.

Grodzinsky E, Ivarsson A, Juto P, et al. New automated immunoassay measuring immunoglobulin A antigliadin antibodies for prediction of celiac disease in childhood. Clin Diagn Lab Immunol. 2001;8(3):564-70. Excluded: Wrong population.

Grodzinsky E, Jansson G, Skogh T, et al. Anti-endomysium and anti-gliadin antibodies as serological markers for coeliac disease in childhood: a clinical study to develop a practical routine. Acta Paediatrica. 1995;84(3):294-8. Excluded: Wrong population.

Gross S, Bakker SF, van Bodegraven AA, et al. Increased IgA glycoprotein-2 specific antibody titres in refractory celiac disease. J Gastrointestin Liver Dis. 2014;23(2):127-33. Excluded: Wrong comparator.

Guandalini S, Assiri A. Celiac disease: a review. [Review]. Jama, Pediatr. 2014;168(3):272-8. Excluded: Wrong study design for Key Question.

Hadjivassiliou M, Kandler RH, Chattopadhyay AK, et al. Dietary treatment of gluten neuropathy. Muscle Nerve. 2006;34(6):762-6. Excluded: Wrong study design for Key Question.

Hall NJ, Rubin G, Charnock A. Systematic review: adherence to a gluten-free diet in adult patients with coeliac disease. Aliment Pharmacol Ther. 2009;30(4):315-30. Excluded: Individual study in included systematic review.

Hallert C, Granno C, Hulten S, et al. Living with coeliac disease: controlled study of the burden of illness. Scand J Gastroenterol. 2002;37(1):39-42. Excluded: Wrong comparator.

Hallert C, Svensson M, Tholstrup J, et al. Clinical trial: B vitamins improve health in patients with coeliac disease living on a gluten-free diet. Aliment Pharmacol Ther. 2009;29(8):811-6. Excluded: Wrong comparator.

Harewood GC, Murray JA. Diagnostic approach to a patient with suspected celiac disease: a cost analysis. Digest Dis Sci. 2001;46(11):2510-4. Excluded: Wrong comparator.

Harrison E, Li K-K, Petchey M, et al. Selective measurement of anti-tTG antibodies in coeliac disease and IgA deficiency: an alternative pathway. Postgrad Med J. 2013;89(1047):4-7. Excluded: Individual study in included systematic review.

Heil PM, Volc-Platzer B, Karlhofer F, et al. Transglutaminases as diagnostically relevant autoantigens in patients with gluten sensitivity. J Dtsch Dermatol Ges. 2005;3(12):974-8. Excluded: Wrong study design for Key Question.

Hill I. What are the sensitivity and specificity of serologic tests for celiac disease? Do sensitivity and specificity vary in different populations? Gastroenterology. 2005;128(4 Suppl 1):S25-32. Excluded: Not a study (letter, editorial, non-systematic review article, no original data).

Hill ID. Screening for celiac disease. J Pediatr Gastroenterol Nutr. 2013;57(4):414-5. Excluded: Not a study (letter, editorial, non-systematic review article, no original data).

Hizli S, Karabulut H, Ozdemir O, et al. Sensorineural hearing loss in pediatric celiac patients. Int J Pediatr Otorhinolaryngol. 2011;75(1):65-8. Excluded: Wrong comparator.

Hjelle AM, Apalset E, Mielnik P, et al. Celiac disease and risk of fracture in adults--a review. Osteoporos Int. 2014;25(6):1667-76. Excluded: Wrong study design for Key Question.

Hoffenberg EJ, Bao F, Eisenbarth GS, et al. Transglutaminase antibodies in children with a genetic risk for celiac disease. J Pediatr. 2000;137(3):356-60. Excluded: Wrong comparator.

Hogen Esch CE, Csizmadia GDS, van Hoogstraten IMW, et al. Childhood coeliac disease: towards an improved serological mass screening strategy. Aliment Pharmacol Ther. 2010;31(7):760-6. Excluded: Wrong study design for Key Question.

Hojsak I, Mozer-Glassberg Y, Segal Gilboa N, et al. Celiac disease screening assays for children younger than 3 years of age: the performance of three serological tests. Digest Dis Sci. 2012;57(1):127-32. Excluded: Wrong population.

Appendix A4. Excluded Studies List

Holding S, Wilson F, Spradbery D. Clinical evaluation of the BioPlex 2200 Celiac IgA and IgG Kits - a novel multiplex screen incorporating an integral check for IgA deficiency. J Immunol Methods. 2014;405:29-34. Excluded: Wrong study design for Key Question.

Hope BC, Ameratunga R, Austin PM, et al. Diagnostic utility of modified gliadin peptide antibody assays in New Zealand children. J Pediatr Gastroenterol Nutr. 2013;57(1):43-8. Excluded: Wrong population.

Hopper AD, Cross SS, Sanders DS. Patchy villous atrophy in adult patients with suspected gluten-sensitive enteropathy: is a multiple duodenal biopsy strategy appropriate? Endoscopy. 2008;40(3):219-24. Excluded: Individual study in included systematic review.

Hopper AD, Hadjivassiliou M, Hurlstone DP, et al. What is the role of serologic testing in celiac disease? A prospective, biopsy-confirmed study with economic analysis. Clin Gastroenterol Hepatol. 2008;6(3):314-20. Excluded: Wrong population.

Iagnocco A, Ceccarelli F, Mennini M, et al. Subclinical synovitis detected by ultrasound in children affected by coeliac disease: a frequent manifestation improved by a gluten-free diet. Clin Exp Rheumatol. 2014;32(1):137-42. Excluded: Wrong population.

Iovino P, Pascariello A, Russo I, et al. Difficult diagnosis of celiac disease: diagnostic accuracy and utility of chromo-zoom endoscopy. Gastrointest Endosc. 2013;77(2):233-40. Excluded: Wrong population.

Johnston SD, Rodgers C, Watson RG. Quality of life in screen-detected and typical coeliac disease and the effect of excluding dietary gluten. Eur J Gastroenterol Hepatol. 2004;16(12):1281-6. Excluded: Wrong comparator.

Juby LD, Rothwell J, Axon AT. Lactulose/mannitol test: an ideal screen for celiac disease. Gastroenterology. 1989;96(1):79-85. Excluded: Wrong study design for Key Question.

Kalayci AG, Kansu A, Girgin N, et al. Bone mineral density and importance of a gluten-free diet in patients with celiac disease in childhood. Pediatrics. 2001;108(5):E89. Excluded: Wrong comparator.

Kane EV, Newton R, Roman E. Non-Hodgkin lymphoma and gluten-sensitive enteropathy: estimate of risk using meta-analyses. Cancer Causes Control. 2011;22(10):1435-44. Excluded: Wrong study design for Key Question.

Kappler M, Krauss-Etschmann S, Diehl V, et al. Detection of secretory IgA antibodies against gliadin and human tissue transglutaminase in stool to screen for coeliac disease in children: validation study. BMJ. 2006;332(7535):213-4. Excluded: Wrong study design for Key Question.

Karagiozoglou-Lampoudi T, Zellos A, Vlahavas G, et al. Screening for coeliac disease in preschool Greek children: the feasibility study of a community-based project. Acta Paediatr. 2013;102(7):749-54. Excluded: Wrong study design for Key Question.

Katz KD, Rashtak S, Lahr BD, et al. Screening for celiac disease in a North American population: sequential serology and gastrointestinal symptoms. Am J Gastroenterol. 2011;106(7):1333-9. Excluded: Wrong comparator.

Kaukinen K, Collin P, Mykkanen AH, et al. Celiac disease and autoimmune endocrinologic disorders. Dig Dis Sci. 1999;44(7):1428-33. Excluded: Individual study in included systematic review.

Kaukinen K, Salmi J, Lahtela J, et al. No effect of gluten-free diet on the metabolic control of type 1 diabetes in patients with diabetes and celiac disease. Retrospective and controlled prospective survey. Diabetes Care. 1999;22(10):1747-8. Excluded: Wrong outcome.

Kaukinen K, Salmi T, Collin P, et al. Clinical trial: gluten microchallenge with wheat-based starch hydrolysates in coeliac disease patients - a randomized, double-blind, placebo-controlled study to evaluate safety. Aliment Pharmacol Ther. 2008;28(10):1240-8. Excluded: Wrong intervention.

Kemppainen T, Kroger H, Janatuinen E, et al. Osteoporosis in adult patients with celiac disease. Bone. 1999;24(3):249-55. Excluded: Wrong comparator.

Kingstone K, Gillett HR. Lactulose-mannitol intestinal permeability test: a useful screening test for adult coeliac disease. Ann Clin Biochem. 2001;38(Pt 4):415-6. Excluded: Not a study (letter, editorial, non-systematic review article, no original data).

Kocna P, Vanickova Z, Perusicova J, et al. Tissue transglutaminase-serology markers for coeliac disease. Clin Chem Lab Med. 2002;40(5):485-92. Excluded: Wrong study design for Key Question.

Kolek A, Fischerova E, Kos V, et al. Application of ELISA method to determine antigliadin antibodies in children with coeliac disease. Acta Univ Palacki Olomuc Fac Med. 1989;122:183-92. Excluded: Wrong study design for Key Question.

Koletzko S, Burgin-Wolff A, Koletzko B, et al. Prevalence of coeliac disease in diabetic children and adolescents. A multicentre study. Eur J Pediatr. 1988;148(2):113-7. Excluded: Wrong study design for Key Question.

Koop I, Ilchmann R, Izzi L, et al. Detection of autoantibodies against tissue transglutaminase in patients with celiac disease and dermatitis herpetiformis. Am J Gastroenterol. 2000;95(8):2009-14. Excluded: Wrong population.

Appendix A4. Excluded Studies List

Korponay-Szabo IR, Szabados K, Pusztai J, et al. Population screening for coeliac disease in primary care by district nurses using a rapid antibody test: diagnostic accuracy and feasibility study. BMJ. 2007;335(7632):1244-7. Excluded: Wrong study design for Key Question.

Kratzer W, Kibele M, Akinli A, et al. Prevalence of celiac disease in Germany: a prospective follow-up study. World J Gastroenterol. 2013;19(17):2612-20. Excluded: Wrong study design for Key Question.

Kurppa K, Ashorn M, Iltanen S, et al. Celiac disease without villous atrophy in children: a prospective study. J Pediatr. 2010;157(3):373-80. Excluded: Wrong comparator.

Kurppa K, Lindfors K, Collin P, et al. Antibodies against deamidated gliadin peptides in early-stage celiac disease. J Clin Gastroenterol. 2011;45(8):673-8. Excluded: Wrong population.

Lagerqvist C, Ivarsson A, Juto P, et al. Screening for adult coeliac disease - which serological marker(s) to use? J Intern Med. 2001;250(3):241-8. Excluded: Wrong study design for Key Question.

Lahdeaho ML, Kaukinen K, Laurila K, et al. Glutenase ALV003 attenuates gluten-induced mucosal injury in patients with celiac disease. Gastroenterology. 2014;146(7):1649-58. Excluded: Wrong intervention.

Lahteenoja H, Toivanen A, Raiha I, et al. Salivary antigliadin and antiendomysium antibodies in coeliac disease. Scand J Immunol. 1999;50(5):528-35. Excluded: Wrong study design for Key Question.

Leach ST, Aurangzeb B, Day AS. Coeliac disease screening in children: assessment of a novel anti-gliadin antibody assay. J Clin Lab Anal. 2008;22(5):327-33. Excluded: Wrong population.

Lebwohl B, Genta RM, Kapel RC, et al. Procedure volume influences adherence to celiac disease guidelines. Eur J Gastroenterol Hepatol. 2013;25(11):1273-8. Excluded: Individual study in included systematic review.

Lebwohl B, Granath F, Ekbom A, et al. Mucosal healing and mortality in coeliac disease. Aliment Pharmacol Ther. 2013;37(3):332-9. Excluded: Wrong comparator.

Lebwohl B, Hassid B, Ludwin S, et al. Increased sedation requirements during endoscopy in patients with celiac disease. Dig Dis Sci. 2012;57(4):994-9. Excluded: Individual study in included systematic review.

Lebwohl B, Kapel RC, Neugut AI, et al. Adherence to biopsy guidelines increases celiac disease diagnosis. Gastrointest Endosc. 2011;74(1):103-9. Excluded: Individual study in included systematic review.

Leon F, Camarero C, R-Pena R, et al. Anti-transglutaminase IgA ELISA: clinical potential and drawbacks in celiac disease diagnosis. Scand J Gastroenterol. 2001;36(8):849-53. Excluded: Wrong study design for Key Question.

Leon F, Eiras P, Roy G, et al. Intestinal intraepithelial lymphocytes and anti-transglutaminase in a screening algorithm for coeliac disease. Gut. 2002;50(5):740-1. Excluded: Not a study (letter, editorial, non-systematic review article, no original data).

Levinson-Castiel R, Hartman C, Morgenstern S, et al. The role of duodenal bulb biopsy in the diagnosis of celiac disease in children. J Clin Gastroenterol. 2011;45(1):26-9. Excluded: Individual study in included systematic review.

Lewis NR, Scott BB. Systematic review: the use of serology to exclude or diagnose coeliac disease (a comparison of the endomysial and tissue transglutaminase antibody tests). Aliment Pharmacol Ther. 2006;24(1):47-54. Excluded: Systematic review or meta-analysis used as source document only to identify individual studies.

Lewis NR, Scott BB. Meta-analysis: deamidated gliadin peptide antibody and tissue transglutaminase antibody compared as screening tests for coeliac disease. Aliment Pharmacol Ther. 2010;31(1):73-81. Excluded: Individual study in included systematic review.

Liao Z, Gao R, Xu C, et al. Indications and detection, completion, and retention rates of small-bowel capsule endoscopy: a systematic review. Gastrointest Endosc. 2010;71(2):280-6. Excluded: Individual study in included systematic review.

Liu E, Li M, Bao F, et al. Need for quantitative assessment of transglutaminase autoantibodies for celiac disease in screening-identified children. J Pediatr. 2005;146(4):494-9. Excluded: Wrong study design for Key Question.

Lock RJ, Stevens S, Pitcher MCL, et al. Is immunoglobulin A anti-tissue transglutaminase antibody a reliable serological marker of coeliac disease? Eur J Gastroenterol Hepatol. 2004;16(5):467-70. Excluded: Wrong population.

Lorini R, Scotta MS, Cortona L, et al. Celiac disease and type I (insulin-dependent) diabetes mellitus in childhood: follow-up study. J Diabetes Complications. 1996;10(3):154-9. Excluded: Wrong study design for Key Question.

Ludvigsson JF, Pathak J, Murphy S, et al. Use of computerized algorithm to identify individuals in need of testing for celiac disease. J Am Med Inform Assoc. 2013;20(e2):e306-10. Excluded: Wrong study design for Key Question.

Lurz E, Scheidegger U, Spalinger J, et al. Clinical presentation of celiac disease and the diagnostic accuracy of serologic markers in children. Eur J Pediatr. 2009;168(7):839-45. Excluded: Wrong study design for Key Question.

Appendix A4. Excluded Studies List

Lytton SD, Antiga E, Pfeiffer S, et al. Neo-epitope tissue transglutaminase autoantibodies as a biomarker of the gluten sensitive skin disease--dermatitis herpetiformis. Clin Chim Acta. 2013;415:346-9. Excluded: Wrong intervention.

Maki M, Hallstrom O, Vesikari T, et al. Evaluation of a serum IgA-class reticulin antibody test for the detection of childhood celiac disease. J Pediatr. 1984;105(6):901-5. Excluded: Wrong study design for Key Question.

Mankai A, Sakly W, Landolsi H, et al. Tissue transglutaminase antibodies in celiac disease, comparison of an enzyme linked immunosorbent assay and a dot blot assay. Pathol Biol (Paris). 2005;53(4):204-9. Excluded: Wrong population.

Mascart-Lemone F, Lambrechts A. Serology of coeliac disease: early diagnosis and therapeutic impact. Acta Gastroenterol Belg. 1995;58(5-6):388-96. Excluded: Wrong study design for Key Question.

Mascart-Lemone F, Van den Broeck J, Cadranel S, et al. Serological aspects of coeliac disease. Acta Gastroenterol Belg. 1992;55(2):200-8. Excluded: Wrong study design for Key Question.

Matuchansky C. Apparently asymptomatic patients with serologic markers of celiac disease and gluten-free diet. Gastroenterology. 2015;148(1):260. Excluded: Not a study (letter, editorial, non-systematic review article, no original data).

Mazure R, Vazquez H, Gonzalez D, et al. Bone mineral affection in asymptomatic adult patients with celiac disease. Am J Gastroenterol. 1994;89(12):2130-4. Excluded: Wrong study design for Key Question.

Mazzarella G, Salvati VM, Iaquinto G, et al. Reintroduction of gluten following flour transamidation in adult celiac patients: a randomized, controlled clinical study. Clin Dev Immunol. 2012;2012:329150. Excluded: Wrong population.

Mazzone L, Reale L, Spina M, et al. Compliant gluten-free children with celiac disease: an evaluation of psychological distress. BMC Pediatr. 2011;11:46. Excluded: Wrong comparator.

McGowan KE, Castiglione DA, Butzner JD. The changing face of childhood celiac disease in north america: impact of serological testing. Pediatrics. 2009;124(6):1572-8. Excluded: Wrong study design for Key Question.

Medical Advisory S. Clinical utility of serologic testing for celiac disease in asymptomatic patients: an evidence-based analysis (Structured abstract). Health Technology Assessment Database. 2014(2). Excluded: Not a study (letter, editorial, non-systematic review article, no original data).

Medical Advisory S. Clinical utility of serologic testing for celiac disease in Ontario (symptomatic patients) (Structured abstract). Health Technology Assessment Database. 2014(2). Excluded: Not a study (letter, editorial, non-systematic review article, no original data).

Miller A, Paspaliaris W, Elliott PR, et al. Anti-transglutaminase antibodies and coeliac disease. Aust N Z J Med. 1999;29(2):239-42. Excluded: Wrong study design for Key Question.

Mooney PD, Hadjivassiliou M, Sanders DS. Coeliac disease. [Review]. BMJ. 2014;348. Excluded: Not a study (letter, editorial, non-systematic review article, no original data).

Moreno M. Celiac disease in children and adolescents. JAMA Pediatr. 2014;168(3):300. Excluded: Wrong study design for Key Question.

Mozo L, Gomez J, Escanlar E, et al. Diagnostic value of anti-deamidated gliadin peptide IgG antibodies for celiac disease in children and IgA-deficient patients. J Pediatr Gastroenterol Ntr. 2012;55(1):50-5. Excluded: Individual study in included systematic review.

Mubarak A, Nikkels P, Houwen R, et al. Reproducibility of the histological diagnosis of celiac disease. Scand J Gastroenterol. 2011;46(9):1065-73. Excluded: Individual study in included systematic review.

Mustalahti K, Collin P, Sievanen H, et al. Osteopenia in patients with clinically silent coeliac disease warrants screening. Lancet. 1999;354(9180):744-5. Excluded: Not a study (letter, editorial, non-systematic review article, no original data).

Mustalahti K, Lohiniemi S, Collin P, et al. Gluten-free diet and quality of life in patients with screen-detected celiac disease. Eff Clin Pract. 2002;5(3):105-13. Excluded: Wrong study design for Key Question.

Nachman F, del Campo MP, Gonzalez A, et al. Long-term deterioration of quality of life in adult patients with celiac disease is associated with treatment noncompliance. Dig Liver Dis. 2010;42(10):685-91. Excluded: Wrong study design for Key Question.

Nachman F, Maurino E, Vazquez H, et al. Quality of life in celiac disease patients: prospective analysis on the importance of clinical severity at diagnosis and the impact of treatment. Dig Liver Dis. 2009;41(1):15-25. Excluded: Wrong comparator.

National Institute for Health and Clinical Excellence Centre for Clinical Practice. Coeliac disease: recognition and assessment of coeliac disease. 2009. Excluded: individual study in included systematic review.

Nemec G, Ventura A, Stefano M, et al. Looking for celiac disease: diagnostic accuracy of two rapid commercial assays. Am J Gastroenterol. 2006;101(7):1597-600. Excluded: Wrong study design for Key Question.

Appendix A4. Excluded Studies List

Nenna R, Mennini M, Petrarca L, et al. Immediate effect on fertility of a gluten-free diet in women with untreated coeliac disease. Gut. 2011;60(7):1023-4. Excluded: Wrong study design for Key Question.

Nenna R, Pontone S, Pontone P, et al. Duodenal bulb in celiac adults: the "whether biopsying" dilemma. J Clin Gastroenterol. 2012;46(4):302-7. Excluded: Individual study in included systematic review.

Neves MMPS, Gonzalez-Garcia MB, Nouws HPA, et al. An electrochemical deamidated gliadin antibody immunosensor for celiac disease clinical diagnosis. Analyst. 2013;138(7):1956-8. Excluded: Not a study (letter, editorial, non-systematic review article, no original data).

Nordyke K, Norstrom F, Lindholm L, et al. Health-related quality of life in adolescents with screening-detected celiac disease, before and one year after diagnosis and initiation of gluten-free diet, a prospective nested case-referent study. BMC Public Health. 2013;13:142. Excluded: Wrong study design for Key Question.

Nordyke K, Rosen A, Emmelin M, et al. Internalizing the threat of risk--a qualitative study about adolescents' experience living with screening-detected celiac disease 5 years after diagnosis. Health Qual Life Outcomes. 2014;12(91). Excluded: Wrong study design for Key Question.

Norstrom F, Lindholm L, Sandstrom O, et al. Delay to celiac disease diagnosis and its implications for health-related quality of life. BMC Gastroenterology. 2011;11:118. Excluded: Wrong comparator.

Olen O, Gudjonsdottir AH, Browaldh L, et al. Antibodies against deamidated gliadin peptides and tissue transglutaminase for diagnosis of pediatric celiac disease. J Pediatr Gastroenterol Ntr. 2012;55(6):695-700. Excluded: Individual study in included systematic review.

Olivares M, Castillejo G, Varea V, et al. Double-blind, randomised, placebo-controlled intervention trial to evaluate the effects of Bifidobacterium longum CECT 7347 in children with newly diagnosed coeliac disease. Br J Nutr. 2014;112(1):30-40. Excluded: Wrong intervention.

Paavola A, Kurppa K, Ukkola A, et al. Gastrointestinal symptoms and quality of life in screen-detected celiac disease. Dig Liver Dis. 2012;44(10):814-8. Excluded: Wrong study design for Key Question.

Pais WP, Duerksen DR, Pettigrew NM, et al. How many duodenal biopsy specimens are required to make a diagnosis of celiac disease? Gastrointest Endosc. 2008;67(7):1082-7. Excluded: Individual study in included systematic review.

Parizade M, Bujanover Y, Weiss B, et al. Performance of serology assays for diagnosing celiac disease in a clinical setting. Clin Vaccine Immunol. 2009;16(11):1576-82. Excluded: Wrong population.

Parnanen A, Kaukinen K, Helakorpi S, et al. Symptom-detected and screen-detected celiac disease and adult height: a large cohort study. Eur J Gastroenterol Hepatol. 2012;24(9):1066-70. Excluded: Wrong study design for Key Question.

Pascolo P, Faleschini E, Tonini G, et al. Type 1 diabetes mellitus and celiac disease: usefulness of gluten-free diet. Acta Diabetol. 2013;50(5):821-2. Excluded: Not a study (letter, editorial, non-systematic review article, no original data).

Persliden J, Pettersson HB, Falth-Magnusson K. Small intestinal biopsy in children with coeliac disease: measurement of radiation dose and analysis of risk. Acta Paediatr. 1993;82(3):296-9. Excluded: Individual study in included systematic review.

Perticarari S, Presani G, Trevisan M, et al. Serum IgA and IgG antibodies to alpha-gliadin: comparison between two ELISA methods. Ric Clin Lab. 1987;17(4):323-9. Excluded: Wrong outcome.

Pettersson HB, Falth-Magnusson K, Persliden J, et al. Radiation risk and cost-benefit analysis of a paediatric radiology procedure: results from a national study. Br J Radiol. 2005;78(925):34-8. Excluded: Individual study in included systematic review.

Pinto Sanchez MI, Smecuol E, Vazquez H, et al. Very high rate of misdiagnosis of celiac disease in clinical practice. Acta Gastroenterol Latinoam. 2009;39(4):250-3. Excluded: Individual study in included systematic review.

Pittschieler K, Ladinser B. Coeliac disease: screened by a new strategy. Acta Paediatr Suppl. 1996;412:42-5. Excluded: Wrong study design for Key Question.

Poland DCW, Ceelie H, Dinkelaar RB, et al. Determination of anti-endomysium IgA antibodies in the diagnosis of celiac disease: comparison of a novel ELISA-based assay with conventional immunofluorescence. World J Gastroenterol. 2006;12(17):2779-80. Excluded: Wrong comparator.

Prasad KK, Thapa BR, Nain CK, et al. The frequency of histologic lesion variability of the duodenal mucosa in children with celiac disease. World J Pediatr. 2010;6(1):60-4. Excluded: Individual study in included systematic review.

Ransford RAJ, Hayes M, Palmer M, et al. A controlled, prospective screening study of celiac disease presenting as iron deficiency anemia. J Clin Gastroenterol. 2002;35(3):228-33. Excluded: Wrong study design for Key Question.

Ravelli A, Bolognini S, Gambarotti M, et al. Variability of histologic lesions in relation to biopsy site in gluten-sensitive enteropathy. Am J Gastroenterol. 2005;100(1):177-85. Excluded: Individual study in included systematic review.

Appendix A4. Excluded Studies List

Ress K, Harro J, Uibo O, et al. Use of a fully automated immunoassay for celiac disease screening in a pediatric population. Clin Chem Lab Med. 2011;49(6):983-7. Excluded: Wrong study design for Key Question.

Ring Jacobsson L, Friedrichsen M, Goransson A, et al. Does a Coeliac School increase psychological well-being in women suffering from coeliac disease, living on a gluten-free diet? J Clin Nurs. 2012;21(5-6):766-75. Excluded: Wrong population.

Rokkas T, Niv Y. The role of video capsule endoscopy in the diagnosis of celiac disease: a meta-analysis. Eur J Gastroenterol Hepatol. 2012;24(3):303-8. Excluded: Individual study in included systematic review.

Roldan MB, Barrio R, Roy G, et al. Diagnostic value of serological markers for celiac disease in diabetic children and adolescents. J Pediatr Endocrinol. 1998;11(6):751-6. Excluded: Wrong study design for Key Question.

Roos S, Karner A, Hallert C. Psychological well-being of adult coeliac patients treated for 10 years. Dig Liver Dis. 2006;38(3):177-80. Excluded: Wrong comparator.

Rose C, Howard R. Living with coeliac disease: a grounded theory study. J Hum Nutr Diet. 2014;27(1):30-40. Excluded: Wrong study design for Key Question.

Rostom A, Dube C, Cranney A, et al. The diagnostic accuracy of serologic tests for celiac disease: a systematic review. Gastroenterology. 2005;128(4 Suppl 1):S38-46. Excluded: Systematic review or meta-analysis used as source document only to identify individual studies.

Saadah OI, Zacharin M, O'Callaghan A, et al. Effect of gluten-free diet and adherence on growth and diabetic control in diabetics with coeliac disease. Arch Dis Child. 2004;89(9):871-6. Excluded: Wrong comparator.

Saari A, Harju S, Makitie O, et al. Systematic growth monitoring for the early detection of celiac disease in children. JAMA Pediatr. 2015;169(3):e1525. Excluded: Wrong study design for Key Question.

Sacchetti L, Calcagno G, Ferrajolo A, et al. Discrimination between celiac and other gastrointestinal disorders in childhood by rapid human lymphocyte antigen typing. Clin Chem. 1998;44(8 Pt 1):1755-7. Excluded: Wrong population.

Sacchetti L, Ferrajolo A, Salerno G, et al. Diagnostic value of various serum antibodies detected by diverse methods in childhood celiac disease. Clin Chem. 1996;42(11):1838-42. Excluded: Wrong population.

Sainsbury K, Mullan B, Sharpe L. A randomized controlled trial of an online intervention to improve gluten-free diet adherence in celiac disease. Am J Gastroenterol. 2013;108(5):811-7. Excluded: Wrong intervention.

Sakly W, Bienvenu F, Peretti N, et al. IgA anti-transglutaminase antibodies as a tool for screening atypical forms of coeliac disease in a French at-risk paediatric population. Eur J Gastroenterol Hepatol. 2005;17(2):235-9. Excluded: Wrong study design for Key Question.

Sakly W, Mankai A, Ghdess A, et al. Performance of anti-deamidated gliadin peptides antibodies in celiac disease diagnosis. Clin Res Hepatol Gastroenterol. 2012;36(6):598-603. Excluded: Individual study in included systematic review.

Salmaso C, Ocmant A, Pesce G, et al. Comparison of ELISA for tissue transglutaminase autoantibodies with antiendomysium antibodies in pediatric and adult patients with celiac disease. Allergy. 2001;56(6):544-7. Excluded: Wrong population.

Sardy M, Odenthal U, Karpati S, et al. Recombinant human tissue transglutaminase ELISA for the diagnosis of gluten-sensitive enteropathy. Clin Chem. 1999;45(12):2142-9. Excluded: Wrong study design for Key Question.

Sategna-Guidetti C, Grosso SB, Grosso S, et al. The effects of 1-year gluten withdrawal on bone mass, bone metabolism and nutritional status in newly-diagnosed adult coeliac disease patients. Aliment Pharmacol Ther. 2000;14(1):35-43. Excluded: Wrong study design for Key Question.

Sethi GR, Singhal KK, Puri AS, et al. Benefit of gluten-free diet in idiopathic pulmonary hemosiderosis in association with celiac disease. Pediatr Pulmonol. 2011;46(3):302-5. Excluded: Wrong population.

Shah S, Akbari M, Vanga R, et al. Patient perception of treatment burden is high in celiac disease compared with other common conditions. Ame J Gastroenterol. 2014;109(9):1304-11. Excluded: Wrong study design for Key Question.

Shamir R, Yehezkely-Schildkraut V, Hartman C, et al. Population screening for celiac disease: follow up of patients identified by positive serology. J Gastroenterol Hepatol. 2007;22(4):532-5. Excluded: Individual study in included systematic review.

Sharma A, Mews C, Jevon G, et al. Duodenal bulb biopsy in children for the diagnosis of coeliac disease: experience from Perth, Australia. J Paediatr Child Health. 2013;49(3):210-4. Excluded: Individual study in included systematic review.

Siegel M, Garber ME, Spencer AG, et al. Safety, tolerability, and activity of ALV003: results from two phase 1 single, escalating-dose clinical trials. Dig Dis Sci. 2012;57(2):440-50. Excluded: Wrong population.

Smecuol E, Hwang HJ, Sugai E, et al. Exploratory, randomized, double-blind, placebo-controlled study on the effects of Bifidobacterium infantis natren life start strain super strain in active celiac disease. J Clin Gastroenterol. 2013;47(2):139-47. Excluded: Wrong intervention.

Appendix A4. Excluded Studies List

Srinivas M, Basumani P, Podmore G, et al. Utility of testing patients, on presentation, for serologic features of celiac disease. Clin Gastroenterol Hepatol. 2014;12(6):946-52. Excluded: Individual study in included systematic review.

Stern M, Teuscher M, Wechmann T. Serological screening for coeliac disease: methodological standards and quality control. Acta Paediatr Suppl. 1996;412:49-51. Excluded: Wrong study design for Key Question.

Sugai E, Hwang HJ, Vazquez H, et al. New serology assays can detect gluten sensitivity among enteropathy patients seronegative for anti-tissue transglutaminase. Clin Chem. 2010;56(4):661-5. Excluded: Individual study in included systematic review.

Swallow K, Wild G, Sargur R, et al. Quality not quantity for transglutaminase antibody 2: the performance of an endomysial and tissue transglutaminase test in screening coeliac disease remains stable over time. Clin Exp Immunol. 2013;171(1):100-6. Excluded: Individual study in included systematic review.

Swift GL, Smith PM, King L. Screening test for coeliac disease.[Erratum appears in Lancet 1997 Aug 9;350(9075):450]. Lancet. 1997;349(9060):1254. Excluded: Not a study (letter, editorial, non-systematic review article, no original data).

Tack GJ, van de Water JMW, Bruins MJ, et al. Consumption of gluten with gluten-degrading enzyme by celiac patients: a pilot-study. World J Gastroenterol. 2013;19(35):5837-47. Excluded: Wrong population.

Toftedal P, Nielsen C, Madsen JT, et al. Positive predictive value of serological diagnostic measures in celiac disease. Clin Chem Lab Med. 2010;48(5):685-91. Excluded: Wrong study design for Key Question.

Tontini GE, Rondonotti E, Saladino V, et al. Impact of gluten withdrawal on health-related quality of life in celiac subjects: an observational case-control study. Digestion. 2010;82(4):221-8. Excluded: Wrong study design for Key Question.

Tosco A, Auricchio R, Aitoro R, et al. Intestinal titres of anti-tissue transglutaminase 2 antibodies correlate positively with mucosal damage degree and inversely with gluten-free diet duration in coeliac disease. Clin Exp Immunol. 2014;177(3):611-7. Excluded: Wrong population.

Trevisiol C, Ventura A, Baldas V, et al. A reliable screening procedure for coeliac disease in clinical practice. Scand J Gastroenterol. 2002;37(6):679-84. Excluded: Wrong population.

Tursi A, Giorgetti GM, Iani C, et al. Peripheral neurological disturbances, autonomic dysfunction, and antineuronal antibodies in adult celiac disease before and after a gluten-free diet. Dig Dis Sci. 2006;51(10):1869-74. Excluded: Wrong study design for Key Question.

Uenishi RH, Gandolfi L, Almeida LM, et al. Screening for celiac disease in 1st degree relatives: a 10-year follow-up study. BMC Gastroenterology. 2014;14:36. Excluded: Wrong study design for Key Question.

Ukkola A, Maki M, Kurppa K, et al. Diet improves perception of health and well-being in symptomatic, but not asymptomatic, patients with celiac disease. Clin Gastroenterol Hepatol. 2011;9(2):118-23. Excluded: Wrong study design for Key Question.

Usai P, Manca R, Cuomo R, et al. Effect of gluten-free diet and co-morbidity of irritable bowel syndrome-type symptoms on health-related quality of life in adult coeliac patients. Dig Liver Dis. 2007;39(9):824-8. Excluded: Wrong comparator.

Usai P, Minerba L, Marini B, et al. Case control study on health-related quality of life in adult coeliac disease. Dig Liver Dis. 2002;34(8):547-52. Excluded: Wrong study design for Key Question.

Valdimarsson T, Toss G, Ross I, et al. Bone mineral density in coeliac disease. Scand J Gastroenterol. 1994;29(5):457-61. Excluded: Wrong study design for Key Question.

van der Windt D, Jellema P, Mulder CJ, et al. Diagnostic testing for celiac disease among patients with abdominal symptoms: a systematic review. JAMA. 2010;303(17):1738-46. Excluded: Individual study in included systematic review.

Van Meensel B, Hiele M, Hoffman I, et al. Diagnostic accuracy of ten second-generation (human) tissue transglutaminase antibody assays in celiac disease. Clin Chem. 2004;50(11):2125-35. Excluded: Individual study in included systematic review.

Vasquez H, Mazure R, Gonzalez D, et al. Risk of fractures in celiac disease patients: a cross-sectional, case-control study. Am J Gastroenterol. 2000;95(1):183-9. Excluded: Wrong study design for Key Question.

Vere CC, Rogoveanu I, Streba CT, et al. The role of capsule endoscopy in the detection of small bowel disease. Chirurgia (Bucur). 2012;107(3):352-60. Excluded: Individual study in included systematic review.

Vermeersch P, Coenen D, Geboes K, et al. Use of likelihood ratios improves clinical interpretation of IgA anti-tTG antibody testing for celiac disease. Clin Chim Acta. 2010;411(1-2):13-7. Excluded: Individual study in included systematic review.

Vermeersch P, Geboes K, Marien G, et al. Diagnostic performance of IgG anti-deamidated gliadin peptide antibody assays is comparable to IgA anti-tTG in celiac disease. Clin Chim Acta. 2010;411(13-14):931-5. Excluded: Individual study in included systematic review.

Vermeersch P, Geboes K, Marien G, et al. Serological diagnosis of celiac disease: comparative analysis of different strategies. Clin Chim Acta. 2012;413(21-22):1761-7. Excluded: Individual study in included systematic review.

Appendix A4. Excluded Studies List

Viljamaa M, Collin P, Huhtala H, et al. Is coeliac disease screening in risk groups justified? A fourteen-year follow-up with special focus on compliance and quality of life. Aliment Pharmacol Ther. 2005;22(4):317-24. PMID: 16097998. Excluded: Wrong study design for Key Question.

Vilppula A, Kaukinen K, Luostarinen L, et al. Clinical benefit of gluten-free diet in screen-detected older celiac disease patients. BMC Gastroenterology. 2011;11:136. Excluded: Wrong study design for Key Question.

Vogelsang H, Genser D, Wyatt J, et al. Screening for celiac disease: a prospective study on the value of noninvasive tests. Am J Gastroenterol. 1995;90(3):394-8. Excluded: Wrong population.

Volta U, Caio G, Stanghellini V, et al. The changing clinical profile of celiac disease: a 15-year experience (1998-2012) in an Italian referral center. BMC Gastroenterol. 2014;14(1):194. Excluded: Wrong study design for Key Question.

Vriezinga SL, Auricchio R, Bravi E, et al. Randomized feeding intervention in infants at high risk for celiac disease. New Engl J Med. 2014;371(14):1304-15. Excluded: Wrong population.

Walters JR, Banks LM, Butcher GP, et al. Detection of low bone mineral density by dual energy x ray absorptiometry in unsuspected suboptimally treated coeliac disease. Gut. 1995;37(2):220-4. Excluded: Wrong study design for Key Question.

Wang C, Rasmussen H, Perrow W, et al. Larazotide acetate, a first in-class, novel tight junction regulator, meets primary endpoint and significantly reduces signs and symptoms of celiac disease in patients on a gluten-free diet: Results of a multicenter, randomized, placebo controlled trial. Gastroenterology.146(5 SUPPL. 1):S-159. Excluded: Wrong comparator.

Weir DC, Glickman JN, Roiff T, et al. Variability of histopathological changes in childhood celiac disease. Am J Gastroenterol. 2010;105(1):207-12. Excluded: Individual study in included systematic review.

Zanini B, Magni A, Caselani F, et al. High tissue-transglutaminase antibody level predicts small intestinal villous atrophy in adult patients at high risk of celiac disease. Dig Liver Dis. 2012;44(4):280-5. Excluded: Individual study in included systematic review.

Systematic Reviews

Criteria:

- Comprehensiveness of sources considered/search strategy used.
- Standard appraisal of included studies.
- Validity of conclusions.
- Recency and relevance are especially important for systematic reviews.

Definition of ratings from above criteria:

Good: Recent, relevant review with comprehensive sources and search strategies; explicit and relevant selection criteria; standard appraisal of included studies; and valid conclusions.
Fair: Recent, relevant review that is not clearly biased but lacks comprehensive sources and search strategies.
Poor: Outdated, irrelevant, or biased review without systematic search for studies, explicit selection criteria, or standard appraisal of studies.

Case-Control Studies

Criteria:

- Accurate ascertainment of cases
- Nonbiased selection of cases/controls with exclusion criteria applied equally to both.
- Response rate.
- Diagnostic testing procedures applied equally to each group.
- Measurement of exposure accurate and applied equally to each group.
- Appropriate attention to potential confounding variables.

Definition of ratings based on criteria above:

Good: Appropriate ascertainment of cases and nonbiased selection of case and control participants; exclusion criteria applied equally to cases and controls; response rate equal to or greater than 80 percent; diagnostic procedures and measurements accurate and applied equally to cases and controls; and appropriate attention to confounding variables.
Fair: Recent, relevant, without major apparent selection or diagnostic work-up bias but with response rate less than 80 percent or attention to some but not all important confounding variables.
Poor: Major selection or diagnostic work-up biases, response rates less than 50 percent, or inattention to confounding variables.

Randomized, Controlled Trials and Cohort Studies

Criteria:

- Initial assembly of comparable groups:
  - For RCTs: adequate randomization, including first concealment and whether potential confounders were distributed equally among groups.
  - For cohort studies: consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts.
- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination).
- Important differential loss to follow-up or overall high loss to followup.
- Measurements: equal, reliable, and valid (includes masking of outcome assessment).

- Clear definition of interventions.
- All important outcomes considered.
- Analysis: adjustment for potential confounders for cohort studies, or intention to treat analysis for RCTs.

Definition of ratings based on above criteria:
Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (follow-up at least 80 percent); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis. In addition, for RCTs, intention to treat analysis is used.
Fair: Studies will be graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention to treat analysis is done for RCTs.
Poor: Studies will be graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.

Diagnostic Accuracy Studies

Criteria:
- Screening test relevant, available for primary care, adequately described.
- Study uses a credible reference standard, performed regardless of test results.
- Reference standard interpreted independently of screening test.
- Handles indeterminate results in a reasonable manner.
- Spectrum of patients included in study.
- Sample size.
- Administration of reliable screening test.

Definition of ratings based on above criteria:
Good: Evaluates relevant available screening test; uses a credible reference standard; interprets reference standard independently of screening test; reliability of test assessed; has few or handles indeterminate results in a reasonable manner; includes large number (more than 100) broad-spectrum patients with and without disease.
Fair: Evaluates relevant available screening test; uses reasonable although not best standard; interprets reference standard independent of screening test; moderate sample size (50 to 100 subjects) and a "medium" spectrum of patients.
Poor: Has fatal flaw such as: Uses inappropriate reference standard; screening test improperly administered; biased ascertainment of reference standard; very small sample size or very narrow selected spectrum of patients.

Source: U.S Preventive Services Task Force. Procedure Manual. Accessed at http://www.uspreventiveservicestaskforce.org/Page/Name/procedure-manual.

Appendix A6. Reviewers of the Draft Report

Carlo Catassi, MD
Professor of Pediatrics, Università Politecnica dele Marche, Italy

Ivor Hill, MB, ChB, MD
Professor of Clinical Pediatrics, Section Chief Pediatric Gastroenterology, Ohio State University College of Medicine and Nationwide Children's Hospital

Ciaran P. Kelly, MD
Professor of Medicine, Harvard Medical School; Director, Celiac Center, Beth Israel Deaconess Medical Center

Kalle Kurppa, MD, MPH
Tampere Centre for Child Health Research, University of Tampere and Tampere University Hospital, Finland

John Marshall, MD, MSc, FRCPC, AGAF
Professor of Medicine, Division of Gastroenterology, McMaster University, Canada

Appendix B1. Systematic Review of Diagnostic Accuracy Studies

Study, year	Aims	Databases searched; Literature search dates; Other data sources	Eligibility criteria	Patients/studies	Characteristics of identified articles: study designs	Characteristics of identified articles: populations
Maglione, 2016[35]	To assess the evidence on the comparative accuracy and safety of tests used to diagnose celiac disease, including serologic tests, HLA typing, video capsule endoscopy, and endoscopic duodenal biopsy.	Databases: PubMed, Embase, Cochrane Library, and Web of Science Search dates: 1990 to 2015 Additional data sources: Unpublished data were requested by the AHRQ-funded Scientific Resource Center and from manufacturers of all 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 subjects, enrolled a consecutive or random sample, and included ≥300 patients (unless it assessed a special population), and 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 were newly published and not included in the systematic reviews) Sample sizes ranged from 62 to >12,000	Systematic reviews: 10 Controlled trials: 0 Cohorts: 16 Case-control: 7	1 study in US, 3 in UK, 5 in the Middle East, 1 in India, and rest in continental Europe Race/ethnicity rarely described All studies included symptomatic patients or those 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

Study, year	Characteristics of identified articles: interventions	Pooled results	Conclusion	Quality
Maglione, 2016[35]	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 typing: no evidence in general population (2 studies in special populations) Algorithms: 8 original studies	**Video capsule endoscopy** Sensitivity: 89.0% (95% CI, 82.0%-94.0%) Specificity: 95.0% (95% CI, 89.0%-99.0%) LR+: 12.9 (95% CI, 2.9-57.6) LR-: 0.16 (95% CI, 0.10-0.25) **tTG** Sensitivity: 92.8% (95% CI, 90.3%-94.8%) Specificity: 97.9% (95% CI, 96.4%-98.8%) LR+: 45.1 (95% CI, 25.1-75.5) LR-: 0.07 (95% CI, 0.05-0.10) **EMA** Sensitivity: 73.0% (95% CI, 61.0%-83.0%) Specificity: 99.0% (95% CI, 98.0%-99.0%) LR+: 65.6 (95% CI, 35.6-120.8) LR-: 0.28 (95% CI, 0.17-0.41) **DGP** Sensitivity: 87.8% (95% CI, 85.6%-89.9%) Specificity: 94.1% (95% CI, 92.5%-95.5%) LR+: 13.3 (95% CI, 9.6-18.4) LR-: 0.12 (95% CI, 0.08-0.18) **HLA typing** No evidence **Algorithms using ≥1 tests** Insufficient evidence due to heterogeneity	tTG, EMA, DGP, and video capsule endoscopy are all highly accurate. Additional studies are needed on accuracy of algorithms and accuracy of testing in special populations.	Good

Abbreviations: AHRQ=Agency for Healthcare Research and Quality; CD=celiac disease; DGP=deamidated gliadin peptide; EMA=endomysial antibody; HLA=human leukocyte antigen; tTG=tissue transglutaminase; UK=United Kingdom; US=United States.

Appendix B2. Quality Assessment of Systematic Review of Diagnostic Accuracy Studies

Study, Year	Search dates	Search methods reported	Comprehensive search	Inclusion criteria reported	Selection bias avoided	Validity criteria reported	Validity assessed appropriately	Methods used to combine studies reported	Findings combined appropriately	Conclusions supported by data	Quality
Maglione, 2016[35]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good

Appendix B3. Diagnostic Accuracy Studies in Asymptomatic Populations

Study, Year	Type of study	Screening tests	Reference standard	Setting	Screener	Age of enrollees	N	Proportion with condition	Subjects
Mansour, 2011[40]	Cross-sectional	tTG IgA, tTG IgG, EMA IgA, AGA IgA, and AGA IgG	Biopsy	University Hospital Iraq	NR	Mean age, 23.4 years (range, 8 to 42 years)	62	Marsh 3 a-c: 11.3% (7/62)	Type 1 diabetes patients with no symptoms associated with celiac disease and no family history of celiac disease or thyroid disorders
Nevoral, 2014[37]	Cross-sectional	tTG IgA and EMA IgA	Biopsy	Single pediatric department Czech Republic	NR	Range, 16 months-19 years	345 (158 asymptomatic)	Marsh 2 or 3: Asymptomatic, 78.5% (124/158) All children, 76% (263/345)	Children and adolescents examined for suspected celiac disease

Study, Year	Sensitivity	Specificity	AUROC	Quality
Mansour, 2011[40]	tTG IgA: 71% tTG IgG: 57% EMA IgA: 71% AGA IgA: 57% AGA IgG: 57%	tTG IgA: 93% tTG IgG: 93% EMA IgA: 96% AGA IgA: 98% AGA IgG: 98%	NR	Fair
Nevoral, 2014[37]	tTG IgA >10 ULN and positive EMA test: 67% **Subgroups** First-degree relatives (n=32): 70% Type 1 diabetes mellitus (n=40): 64%	tTG IgA >10 ULN and positive EMA test: 83% **Subgroups** First-degree relatives (n=32): 81% Type 1 diabetes mellitus (n=40): 93%	NR	Fair

Abbreviations: AGA=antigliadin antibodies; AUROC=area under the receiver operating curve; EMA=endomysial antibody; IgA=immunoglobulin A; IgG=immunoglobulin G; NR=not reported; tTG=tissue transglutaminase; ULN=upper limit of normal.

Appendix B4. Quality Assessment of Diagnostic Accuracy Studies in Asymptomatic Populations

Study, year	Appropriate spectrum of patients	Adequate sample size (>500)	Credible reference standard used	Reference standard applied to all patients	Screening test adequately described	Reference standard interpreted independently	Quality
Mansour, 2011[40]	Unclear	No	Yes; biopsy	Yes	Yes	Unclear	Fair
Nevoral, 2014[37]	Unclear	No	Yes; biopsy	Yes	Yes	Unclear	Fair

Appendix B5. Randomized, Controlled Trial of Treatment

Author, year	Study design	No. of centers, Country	Study duration Mean followup	Interventions	Patient characteristics	Inclusion/Exclusion criteria	Number screened Number eligible Number enrolled Number analyzed Withdrawals Loss to followup
Kurppa, 2014[59]	RCT	1 center Finland	1 year followup	A. Gluten diet (n=20) B. Gluten-free diet (GFD) group (n=20) Note: 1 person in group A started a gluten-free diet soon after randomization, but was analyzed in the gluten group due to the intention-to-treat analysis.	A vs. B Median age (range): 42 (23-62) vs. 42 (21-74) % female: 25% vs. 45% Hypothyroidism: 10% vs. 5% Other chronic condition: 35% vs. 35% Osteoporotic fracture: 0% vs. 0% Females: Infertility or frequent miscarriages: 20% vs. 11% Median age at menarche (range): 13 (13-15) vs. 13 (9-14) years	Targeted screening (recruited relatives of celiac patients). Included EMA-positive adults (ages 18-75 years) who considered themselves asymptomatic (defined as an absence of: abdominal pain [>3 episodes over ≥3 months interfering with function], constipation [<3 bowel movements per week or difficulty during defecation], and diarrhea [≥3 loose stools/day], and extra-intestinal 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. Excluded those with a previous diagnosis of celiac disease, age <18 years, evident clinical symptoms, dietary gluten restriction, severe contemporary illness or immunosuppressive medication, or ongoing or planned pregnancy.	Screened: 3,031 at-risk volunteers Eligible: 40 Enrolled: 40 Analyzed: 40 Withdrawals or loss to followup: None

Appendix B5. Randomized, Controlled Trial of Treatment

Author, year	Outcomes assessed	Clinical health outcomes	Clinical health outcomes: subgroups	Adverse events	Quality rating	Funding source
Kurppa, 2014[59]	Serology Celiac-related genotyping Gastrointestinal Symptoms Rating Scale (GSRS): 7-point Likert scale, higher score indicates more severe symptoms Psychological General Well-Being (PGWB): 6-point Likert scale, higher score indicates better health-related quality of life Short-Form 36-Item Health Survey (SF-36): 0-100, higher score indicates better health-related quality of life Visual Analogue Scale (VAS): 0-100, higher score indicates better subjective perception of health Laboratory parameters Bone mineral density Body composition Small bowel mucosal morphology and inflammation	<u>Gastrointestional symptoms after 1 year, difference in mean change (95% CI):</u> GSRS Total, -0.4 (-0.7 to -0.1); p=0.003, favors GFD GSRS Diarrhea, -0.6 (-1.1 to 0.0); p=0.052, favors GFD GSRS Indigestion, -0.7 (-1.1 to -0.2); p=0.006, favors GFD GSRS Constipation, -0.1 (-0.5 to 0.3); p=0.325 GSRS Abdominal pain, -0.2 (-0.5 to 0.2); p=0.126 GSRS Reflux, -0.5 (-0.9 to -0.1); p=0.050, favors GFD <u>Psychological general well-being, after 1 year, difference in mean change (95% CI):</u> PGWB Anxiety, 1.6 (0.4 to 2.8); p=0.025, favors GFD PGWB Depression, 0.3 (-0.5 to 1.2); p=0.281 PGWB Well-being, 0.5 (-1.0 to 2.0); p=0.700 PGWB Self-control, 0.3 (-0.7 to 1.4); p=0.775 PGWB General health, 0.7 (-1.0 to 2.4); p=0.532 PGWB Vitality, 0.4 (-1.5 to 2.2); p=0.670 <u>SF-36, after 1 year, difference in mean change (95% CI):</u> SF-36 Physical functioning, -2.8 (-8.2 to 2. 6), p=0.299 SF-36 Role limitations due to physical problems, 2.3 (-12.4 to 17); p= 0.749 SF-36 Role limitations due to emotional problems, 7.2 (-12.6 to 27); p=0.464 SF-36 Vitality, 6.0 (-4.3 to 16.4); p=0.245 SF-36 Mental health, 2.6 (-3.8 to 8.9); p=0.414 SF-36 Social functioning, -8.3 (-15.8 to -0.8); p=0.031, favors gluten group SF-36 Bodily pain, 0.8 (-9.8 to 11.4); p=0.881 SF-36 General health, 2.8 (-7.1 to 12.7); p=0.568 VAS: Improved in the GFD group (p=0.017) <u>Laboratory parameters</u>: Mean blood hemoglobin (SD), g/dL: A. Baseline: 14.3 ± 1.4, Change after 1 year: -0.2 ± 0.6 B. Baseline: 14.4 ± 1.6, Change after 1 year: -0.2 ± 0.7 Mean difference between groups, 0.0 (95% CI, -0.4 to 0.4); p=0.902 Mean serum total iron (SD), micromol/L: A. Baseline: 17.3 ± 5.7, Change after 1 year: 2.8 ± 6.8 B. Baseline: 20.0 ± 8.6, Change after 1 year: 0.3 ± 7.2 Mean difference between groups, -2.5 (95% CI, -7.0 to 2.1); p=0.288	NA	No withdrawals "as a result of major symptoms or complications"	Fair	Academy of Finland Research Council for Health, the Competitive Research Funding of the Pirkanmaa Hospital District, the Sigrid Juselius Foundation, the Finnish Foundation for Gastroenterological Research, the Yrjo Jahnsson Foundation, the Finnish Medical Foundation, the Foundation for Pediatric Research, and the Finnish Celiac Society.

Appendix B5. Randomized, Controlled Trial of Treatment

Author, year	Outcomes assessed	Clinical health outcomes	Clinical health outcomes: subgroups	Adverse events	Quality rating	Funding source
		Body composition: Mean BMI (SD), kg/m^2: A. Baseline: 26.4 ± 3.7, Change after 1 year: -0.3 ± 1.0 B. Baseline: 27.0 ± 6.8, Change after 1 year: 0.0 ± 1.2 Mean difference between groups, 0.3 (95% CI, -0.5 to 1.0); p=0.451 Mean % total body fat (SD): A. Baseline: 28.9 ± 8.2, Change after 1 year: -0.6 ± 2.4 B. Baseline: 34.0 ± 8.9, Change after 1 year: -1.2 ± 3.4 Mean difference between groups, -0.5 (95% CI, -2.4 to 1.4); p=0.600 BMD: Mean lumbar spine (SD), g/cm^2: A. Baseline: 1.17 ± 0.21, Change after 1 year, -0.01 ± 0.03 B. Baseline: 1.17 ± 0.19, Change after 1 year, 0.00 ± 0.02 Mean difference between groups, 0.01 (95% CI, -0.01 to 0.02); p=0.338 Mean femur neck (SD), g/cm^2: A. Baseline: 1.00 ± 0.12, Change after 1 year: -0.1 ± 0.03 B. Baseline: 0.97 ± 0.14 Change after 1 year: 0.00 ± 0.02 Mean difference between groups, 0.01 (95% CI, -0.01 to 0.03); p=0.182				

Abbreviations: BMD=bone mineral density; BMI=body mass index; CI=confidence interval; EMA=endomysial antibody; GFD=gluten-free diet; GSRS=Gastrointenstinal Symptoms Rating Scale; HRQOL=health-related quality of life; NA=not applicable; PGWB=Psychological General Well-Being; RCT=randomized, controlled trial; SD=standard deviation; SF-36=Short-Form 36-Item Health Survey; VAS=visual analogue scale.

Appendix B6. Quality Assessment of Randomized, Controlled Trial of Treatment

Author, year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?	Loss to followup: differential/ high?	Analyze people in the groups in which they were randomized?	Quality
Kurppa, 2014[59]	Yes	Yes	Mostly	Yes	Yes	Not possible	Not possible	Yes	No/No	Yes	Fair