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

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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).

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Structured Abstract

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

Purpose: To review the evidence on screening for CD in asymptomatic adults, adolescents, and children 3 years of age and older for the United States Preventive Services Task Force.

Data Sources: Ovid MEDLINE, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews (to February 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 serological tests for CD.

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 CD. One recent, good-quality systematic review found serological tests to be accurate for diagnosing CD, 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 serological findings found initiation of a gluten-free diet associated with small improvement in gastrointestinal symptoms versus no gluten-free diet (less than 1 point on a 1 to 7 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 and treatment for CD in asymptomatic adults, adolescents, and children; accuracy of screening tests; and optimal screening strategies.

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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 (CD) in adults, adolescents, and children 3 years of age and older. This topic has not previously been reviewed by the USPSTF.

Condition Definition

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

Prevalence

A challenge in estimating prevalence of CD is that in a number of studies, diagnosis was based on serological testing without histological confirmation, potentially overestimating prevalence of CD due to false-positive serological tests. However, a systematic review of 38 studies in North America and Western Europe found that CD prevalence was 0.152 to 1.87 percent in studies that included biopsy confirmation of positive serological tests, and was similar (0.152 to 2.67 percent) 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 CD diagnosed by endomysial antibody (EMA)-positive serology and confirmed by biopsy (<30%) or human leukocyte antigen (HLA) haplotypes DQ2 and DQ8 among 4,126 not-at-risk (average risk) individuals 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 CD using stored sera from a population-based sample of individuals aged 50 and older in Minnesota found that the prevalence of undiagnosed CD was 0.8 percent as defined by initial tissue transglutaminase (tTGA) immunoglobulin (Ig)A 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 aged 6 years or older who participated in the 2009-2010 National Health and Nutrition Examination Survey (NHANES) found the prevalence of CD as defined by positive serology or patient-self report was 0.71 percent among the general population, 0.76 percent among those aged ≥ 20 years, 0.62 percent among women, and 1.01 percent among non-Hispanic whites.⁴ Some data suggests that

the prevalence of CD in the U.S. 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 CD among patients without overt symptoms.)

Etiology, Natural History, and Burden of Disease

CD is caused by an immune response to dietary gluten in genetically susceptible individuals. Specifically, individuals with alleles that encode for HLA-DQ2 and DQ8 proteins are at risk for CD. However, many individuals with these alleles do not develop CD, 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 CD,⁹ more recent literature has not found an association between breastfeeding and risk of CD association.^{10, 11} Gastrointestinal illness may increase the risk of CD in infancy.⁸

CD affects both children and adults. Seroconversion to antibodies associated with CD may occur at any time, and disease progression can take place over months or years.¹² Data suggest that the average age at CD 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 CD is variable among both adults and children. **Classic** CD presents with symptoms of malabsorption, such as diarrhea, abdominal pain, and weight loss. In children, classic CD is characterized by onset of gastrointestinal symptoms and impaired growth between 6 and 24 months of age, but this is now an uncommon presentation.¹⁵ Analysis of trends among 590 patients with biopsy-diagnosed CD in New York from 1981-2004 found that the percentage of those presenting with diarrhea decreased from 91.3 percent before 1980 to 37.2 percent after 2000, perhaps due to increased awareness of CD, increased screening of asymptomatic or mildly symptomatic individuals, and/or ease of serologic testing.¹³ CD now presents more typically with non-gastrointestinal, 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 CD is **subclinical** disease, or disease that is below the threshold of clinical detection, i.e., without signs of common symptoms sufficient to trigger testing for CD.¹⁶ Individuals with subclinical CD may have non-specific symptoms of CD such as fatigue that are not recognized until initiation of a gluten-free diet. **Asymptomatic** or **silent** CD refers to those who have been diagnosed with CD by serologic testing and intestinal biopsy, but do not manifest any common symptoms or signs of CD. **Potential** CD refers to those with and without symptoms who have positive serology, but absent or mild intestinal damage on biopsy. **Latent** CD, a less commonly used term, is used to describe individuals previously diagnosed with CD who have

normal intestinal mucosa on a gluten-free diet or those with normal intestinal mucosa while on a gluten-containing diet who later develop CD.^{16, 17} The natural history of subclinical, asymptomatic, potential, and latent CD is not well-defined, and it is not entirely clear if they represent progressive stages of CD or distinct subtypes.¹⁸ In an Italian retrospective study of 549 patients with CD, 45.7 percent showed classical, 47.7 percent subclinical, and 6.6 percent silent forms of CD at the time of the diagnosis.¹⁹ (See Contextual Question 2 for additional details regarding the natural history of subclinical or silent CD.)

Some evidence suggests that CD 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 U.S. and Europe showed an increased risk for all-cause mortality in those with CD (odds ratio [OR] 1.24, 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, CI 1.02 to 1.31) and non-Hodgkin lymphoma (OR 2.55, CI 1.02 to 6.36). However, some data suggest that asymptomatic or silent CD is not associated with increased mortality or other complications of CD. A retrospective study of 549 patients with CD diagnosed by intestinal biopsy found that the rate of complications on a gluten-free diet for a mean duration 7 years, including malignancy, was highest among those with classic CD (5.58%); no patients with silent disease experienced complications.¹⁹

Non-celiac gluten sensitivity (NCGS) refers to a condition in which individuals with symptoms such as abdominal pain and bloating improve with removal of exposure to gluten, but do not have diagnostic features of CD and are not thought to be at increased risk of nutritional deficiency states or other complications associated with CD.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 and 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 no gluten diets, potentially calling into question the underlying concept for this condition.²²

Risk Factors

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

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

Rationale for Screening/Screening Strategies

Studies in the U.S. and Europe suggest that CD may be underdiagnosed, based on the prevalence of positive serological tests (initial tTG antibody tests followed by EMA testing for those with positive or borderline findings) in persons not previously diagnosed with CD.²⁴ Evidence also suggests that diagnosis of CD is often delayed. A survey of 1,612 patients with CD in the U.S. 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 CD.⁹

Clinical practice guidelines recommend an algorithmic approach to diagnostic testing for CD, starting with IgA tTG and with further testing based on the probability of disease.^{26, 27} IgA anti-tTG is the standard method of testing for CD in individuals older than 2 years. The sensitivity of IgA tTG has been reported at about 95 percent and specificity at 95 percent or greater.²⁶ In patients in whom CD is suspected but IgA deficiency is a consideration, total IgA is measured. Alternatively, IgA testing as well as IgG tTG and/or IgG-deamidated gliadin peptides (DGPs) can be obtained in such patients. Clinical practice guidelines in the U.S. and Europe recommend intestinal biopsy to confirm the diagnosis of CD (e.g., based on presence of villous atrophy classified as grade 3 or higher based on 0 to 4 Marsh criteria), and to distinguish CD from other disorders affecting the small intestine.^{26, 27} Intestinal biopsy may also be performed if clinical suspicion for CD is high, but serologic tests are negative. It has been suggested that a combination of serologic tests could be used to establish CD diagnosis as an alternative to biopsy,^{26, 27} but it is unclear how frequently CD is diagnosed in the absence of biopsy in current clinical practice.²⁸ Rarely, capsule endoscopy is used to establish a diagnosis of CD in patients who are unwilling or unable to undergo upper endoscopy with intestinal biopsy. HLA-DQ2/DQ8 genotyping is not used routinely to diagnose CD, but may be used to rule out the disease in cases with equivocal serologic tests and/or small-bowel histologic findings.

Many individuals initiate a gluten-free diet prior to consultation with a health care provider, which complicates the diagnosis of CD 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 CD before having patients undergo a gluten challenge.²⁶

Anti-gliadin antibodies were previously routinely used to diagnose CD, but are no longer recommended due to inferior sensitivity and specificity compared to newer serologic tests. Likewise, intestinal permeability tests, D-xylose, and small-bowel follow-through are not recommended to diagnose CD.²⁶

Interventions/Treatment

The mainstay of treatment for CD 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 those 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 CD occurs in a minority of patients and is characterized by ongoing symptoms of malabsorption despite adherence to a gluten-free diet for 6 to 12 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 CD among individuals with signs and symptoms of malabsorption as well as certain populations of asymptomatic individuals at increased risk for CD (**Table 1**).^{26, 31-33} Reliable data on the frequency of screening for CD in clinical practice is not available.^{12, 24}

The complex clinical spectrum of CD complicates diagnosis and management. Due to recent media attention to gluten and its potential adverse effects on health, many individuals start a gluten-free diet without medical advice.¹² Some experience improvement in gastrointestinal symptoms that are attributed to CD. As discussed previously, clinical improvement on a gluten-free diet is not diagnostic of CD, 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 the AHRQ determined the scope and key questions for this review. In conjunction with the USPSTF leads and 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 February 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 3 years of age or older without known CD who had not sought evaluation for potential CD, including persons at higher risk due to family history or presence or conditions associated with CD. For treatment, the population of interest was persons with screen-detected CD 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 those 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 USPSTF³⁴ 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", "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 will be reviewed by content experts, USPSTF members, AHRQ Project Officers, and collaborative partners, and posted for public comment.

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 CD 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 CD versus universal screening for CD 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 CD.

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

Summary

One good-quality systematic review found tTG antibody tests associated with high sensitivity and specificity in populations not restricted to asymptomatic persons. Based on new studies, the pooled sensitivity in the systematic review was 92.8 percent (95% CI, 90.3% to 94.8%) and specificity 97.9% (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 serological 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 CD included 56 original studies and 12 prior systematic reviews (**Appendices B1 & 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 testing in adults. One study was conducted in the U.S.,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 (**Appendices 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 tTG IgA was associated with high (>90%) sensitivity and specificity, and EmA IgA tests associated with high specificity, based on consistent results from prior systematic reviews and new studies. For tTG IgA, the pooled sensitivity based on new studies was 92.8% (95% CI, 90.3% to 94.8%) and specificity 97.9% (95% CI, 96.4% to 98.8%), for a PLR of 45.1 (95% CI, 25.1 to 75.5) and NLR of 0.07 (95% CI, 0.05 to 0.10). For EmA IgA testing, the pooled sensitivity based on new studies was 73.0% (95% CI, 61.0% to 83.0%) and specificity 99.0% (95% CI, 98.0% to 99.0%), for a 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 DGP IgA tests indicated somewhat weaker likelihood ratios. For DGP IgA, the pooled sensitivity was 87.8% (95% CI, 85.6% to 89.9%) and specificity was 94.1% (95% CI, 92.5% to 95.5%), for a 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% (95% CI, 82.0% to 94.0%) and specificity 95.0% (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} Sensitivities and specificities were generally similar across age groups, with the exception of one study which reported specificity of 26% among those 18 years of age or younger for the DGP IgA test.³⁸ Sensitivities were 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 (**Appendices B3 and B4**).^{37, 40} A small (n=62), fair-quality study of patients in Iraq with type 1 diabetes mellitus patients (mean age 23 years) without symptoms or a family history of CD evaluated IgA tTG, IgG tTG, IgA EMA, IgA AGA, and IgG AGA assays.⁴⁰ The prevalence of CD based on biopsy was 11.3 percent (7/62); sensitivities ranged from 57 percent for the IgG tTG test to 71 percent for the IgA tTG and IgA EmA tests, resulting in positive predictive values (PPVs) of 50.0 to 71.4 percent; specificities were similar across tests, ranging from 93 to 98 percent, for negative predictive values (NPVs) of 94.4 to 96.4 percent.

Another fair-quality study reported diagnostic accuracy of the combination of IgA tTG and IgA-EMA in a subgroup of 158 asymptomatic Czech children and adolescents, ages 16 months to 19 years, at higher risk for CD because they had a first degree relatives with CD 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 IgA tTG >10 times the upper limit of normal and positive IgA EMA. Results were not reported for the subgroup of patients with Marsh 3 biopsy findings. Sensitivity was 70 percent and specificity 81 percent for patients screened because they had a first-degree relatives (n=32), and sensitivity was 64 percent and specificity 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 a gluten-free diet associated with small improvements in gastrointestinal symptoms (less than 1 point on a 1 to 7 scale) versus no gluten-free diet after 1 year, but there were no changes on most quality of life outcomes. No other study evaluated effects of gluten-free diet 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 adults diagnosed with CD through screening of asymptomatic relatives of persons with CD (**Appendices B5 and B6**).⁵⁹ Median age of participants was 42 years. Diagnosis of CD was based on a positive serum EMA test. Although biopsy was performed, histopathological findings of CD 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 non-gluten-free diet group; 2 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 versus a non-gluten free diet based on the overall Gastrointestinal Symptoms Ratings Scale (difference in mean change -0.4 on a 1 to 7 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 1 to 6 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, mean serum total iron, mean body mass index, mean

percent total body fat, or mean lumbar spine or femoral neck bone mineral density. After 2 years, over 90 percent of subjects reported adherence to the gluten-free diet, and improvements in histopathological findings were observed in the gluten-free diet group at 1 year compared to the non-gluten-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 non-diagnostic (Marsh 1 or 2) histological 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 patient's ratings changing from severe/moderate to slight/no symptoms ($p < 0.05$), versus no changes on a non-gluten-free diet.

Three small (n=14 to 32) studies evaluated effects of a gluten-free diet in asymptomatic adult with CD, but did not meet inclusion criteria because they did not have a non-gluten-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 of 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 study on the effectiveness of treatment of screen-detected CD compared with treatment initiated after clinical diagnosis on morbidity, mortality or quality of life.

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

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

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 CD in the U.S. are not available.

Most prevalence studies of the general population were not designed to determine whether participants had symptoms potentially attributable to CD or whether they were truly asymptomatic. In a large (n=7,798) NHANES study of persons aged 6 years or older, the prevalence of CD as defined by positive IgA TTG and positive IgA endomysial antibodies was 0.71 percent among the general population, 0.76 percent among those 20 years of age 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 CD and whether they were on a gluten-free diet, but were not interviewed regarding symptoms that could be attributed to CD. Other studies of the general adult population in the U.S. found a CD prevalence of 0.2 to 0.9 percent based on positive serologic tests, specifically initial tTGA followed by EMA testing.^{3, 5, 64} None of these studies reported whether participants had symptoms that could be due to CD. Some studies from Europe reported the proportion of patients with CD who were asymptomatic. In an Italian retrospective study of 549 CD patients diagnosed by intestinal biopsy, 45.7 percent of patients presented with classical CD and 6.6 percent were asymptomatic.¹⁹ Another Italian study of patients with CD found that of 770 patients, 79 percent presented with classical CD and 21 percent presented with atypical or silent CD.⁶⁵

Presumably, many cases of CD detected by screening would be subclinical or silent. However, a limitation of many existing studies is that diagnosis of CD was based on positive results on combinations of serologic tests without histological confirmation. However, serologic tests are associated with a small proportion of false-positives in symptomatic persons. At a given diagnostic accuracy, the PPV of serologic tests will be lower in lower CD prevalence populations.^{16, 24}

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

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

Data regarding the proportion of individuals with silent or subclinical CD who later develop symptomatic CD are limited. In a study of stored sera from young adults at Warren Air Force base collected from 1948-1954, none of 14 subjects with undiagnosed CD based on serological tests received a clinical diagnosis of CD 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 CD based on positive IgA EMA and positive/borderline results for IgA TTG, two individuals were clinically diagnosed with CD at mean followup of 31.1 years.⁶⁴ In a study of 16,847 adults aged 50 years or older in Minnesota, 129 were found to have undiagnosed

CD based on positive IgA TTG antibody and positive IgA EMA antibody.³ During median followup of 10.3 years, 20 were clinically diagnosed with CD. A study of 3,654 Finnish children without known celiac disease found that 1.5 percent (56 children) had positive IgA TTG antibody and IgA or IgG EMA tests. Over 7 years of follow-up, 37 (~1%) were diagnosed with celiac disease on the basis of biopsy, of which 10 remained clinically silent.⁶⁸ A Dutch study of children 2 to 4 years of age diagnosed with CD based on EMA antibodies and confirmatory biopsy through a screening program found that 5 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 29 months) with potential CD (serology positive/March 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 CD.⁷⁰

Evidence is conflicting whether individuals diagnosed with subclinical or silent CD experience the same mortality risk as the general population.^{3, 5, 20, 67, 71-74} The Warren Air Force base study discussed above found all-cause mortality higher among those with undiagnosed CD (based on positive serology) after 45 years of followup than seronegative controls within the same cohort.⁵ However, symptom status of those with undiagnosed CD was not reported. In a study of stored sera from German adults collected from 1989 to 1990, positive CD serology was associated with increased risk of all-cause mortality compared to 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 CD was not reported.

A meta-analysis of observational studies reported somewhat conflicting results regarding effects of CD diagnosed by serologic testing and association with increased risk of all-cause mortality and cancer compared to seronegative age and sex-matched controls.²⁰ In three studies screen-detected CD (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 latent CD (positive serology and normal mucosa) associated with estimated excess mortality of 1.7 per 1000 person-years compared with age- and sex-matched controls in the general population (hazard ratio 1.35; 1.14-1.58).⁷⁴ Symptom status was not reported, but the authors noted that clinical suspicion for CD was the only major indication for small intestinal biopsy in Sweden, suggesting that individuals may have been symptomatic.⁷⁴ In another study of screen-detected CD among adults in Northern Ireland, positive serologic tests for CD were not associated with excess mortality risk compared to age-specific mortality in the general population.⁶⁷

Some data suggest that subclinical or silent CD is associated with lower risk of developing CD complications than symptomatic disease (see **Table 2**). An Italian retrospective study of 549 CD patients diagnosed by intestinal biopsy found that the rate of complications on a gluten-free diet (mean duration 7 years, range 1 to 15 years) was 5.58 percent among those with classical CD (n=251) and 1.53 percent among those with subclinical CD (n=262, defined as the presence of gluten-sensitive enteropathy on biopsy with extraintestinal symptoms but no gastrointestinal symptoms).¹⁹ Complications included gastrointestinal adenocarcinoma, Sjögren's disease, jejunal enteropathy-associated T-cell lymphoma, myocardial infarction, sclerosing cholangitis,

herpetiform dermatitis, gastric mucosa-associated lymphoid tissue (MALT) lymphoma, ulcerative jejunitis, severe nonalcoholic steatohepatitis (NASH), 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 CD (histological confirmation) evaluated presentation patterns of patients who developed complicated versus non-complicated CD ($p < 0.001$).⁶⁵ Six patients with classical malabsorption symptoms at presentation developed complications compared to no patients with atypical and subclinical CD over a mean of 5 years ($p < 0.001$). Complications included enteropathy-associated T-cell lymphoma, small bowel carcinoma, and refractory CD.

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 CD in the target populations for this review (adults, adolescents, and children 3 years of age or older). Although serologic tests for CD used in screening appear to be highly accurate, almost all studies on diagnostic accuracy evaluated populations with symptoms of CD or in whom symptom status was not reported. Two studies that specifically evaluated patients who were high risk for CD based on family history or presence of conditions associated with CD reported lower sensitivity and inconsistent specificity.^{37, 40}

Only one randomized trial evaluated the effectiveness of gluten-free diet versus no gluten-free diet in asymptomatic persons with screen-detected CD.⁵⁹ It found initiation of a gluten-free diet in screen-detected, asymptomatic adults associated with improved gastrointestinal symptoms, though effects were relatively small (less than 1 point on a 1 to 7 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 CD and were diagnosed on the basis of serological testing. Histological findings of CD 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 histologically-proven CD. Three small studies on effects of a gluten-free diet in persons with asymptomatic CD 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 study⁶² found increased worry about health following initiation of a gluten-free diet and one study⁶³ 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 initiation delayed until the development of symptoms in asymptomatic persons diagnosed with CD.

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 serological testing in asymptomatic populations, and only one trial of treatment in asymptomatic, screen-detected persons with CD. Although numerous studies evaluated the diagnostic accuracy of tests for CD in patients that 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 CD that do not require histological confirmation. The proportion of patients who are diagnosed with CD or initiate a gluten-free diet based on serological testing alone is unknown, but may be increasing in clinical practice, despite clinical practice guideline recommendations for histological confirmation.

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

A recent randomized trial that screened persons with a first or second degree relative with CD 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 pharmacological treatments for CD,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 U.S., CD is uncommon among racial and ethnic minorities, although it does occur. In an NHANES study, the prevalence of IgA tTGA results were 0.8 percent (27/3430) among non-Hispanic Whites, 0.07 percent (1/1394) among non-Hispanic blacks, 0.03 percent (1/2519) among other Hispanic, not Mexican Americans, and 0.2 percent (1/455) among other races/ethnicities.⁴

The only randomized trial of treatment with a gluten-free diet among asymptomatic screen-detected individuals was restricted to persons younger than 18 or older than 75 years of age.⁸⁰ Although CD is most commonly diagnosed between 40 to 60 years of age,^{13, 14} it can impact 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 CD, 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 serological 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 individuals, and on the effects of immediate initiation upon diagnosis versus initiation delayed until the development of symptoms. The in-

progress Celiac Disease and Diabetes-Dietary Intervention and Evaluation Trial (CD-DIET), which involves screening of children and adults with type 1 diabetes mellitus for asymptomatic CD followed by randomization to a gluten-free or no gluten-free diet, is designed to assess outcomes (including diabetes control, bone mineral density, and health-related quality of life) over 1 year, and should help clarify effects of screening in higher-risk individuals.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 serological findings without histological changes, trials should focus on patients with histological findings of CD, or report analyses stratified according to baseline histological findings. Trials should evaluate populations across the age spectrum, including children, adolescents, and adults, as CD can be diagnosed in any of these age groups.

Research is also needed to better understand the natural history of subclinical and silent CD, including the proportion of patients who develop symptoms, the proportion that develops complications, and the proportion in whom serological and/or histological findings resolve without treatment.

Conclusions

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

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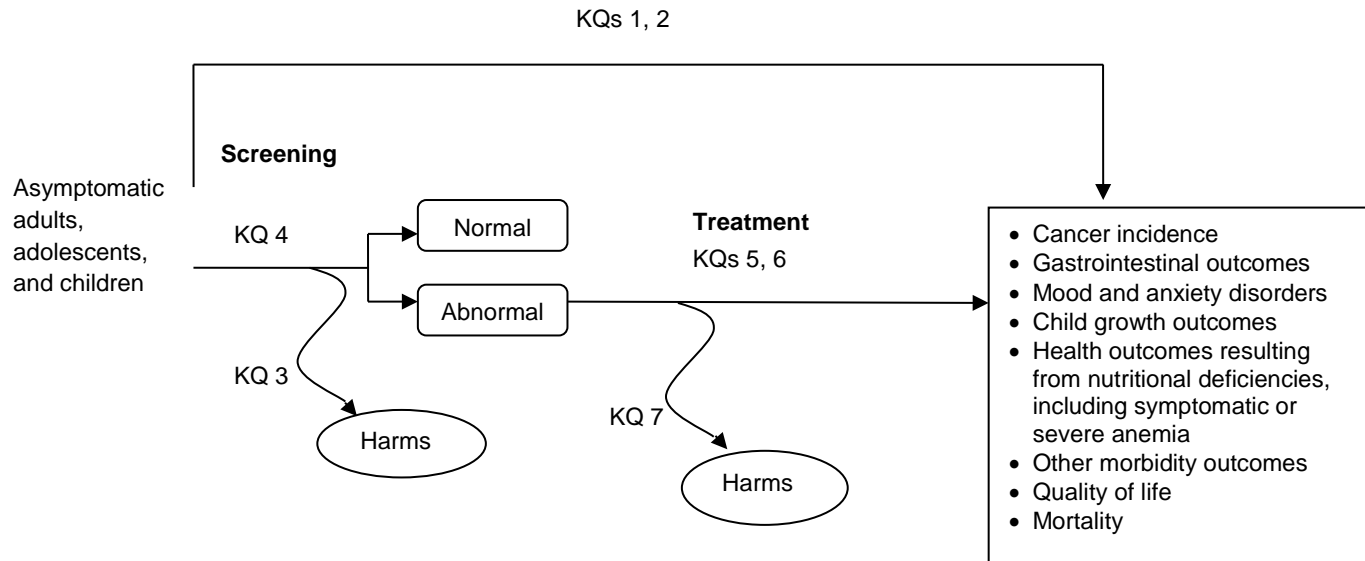
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Figure. Analytic Framework



Abbreviation: KQ = key question.

Table 1. Recommendations of Other Groups

Organization	Screening/Testing Recommendation for Celiac Disease
American College of Gastroenterology ²⁶	<ul style="list-style-type: none"> • Individuals with signs/symptoms of malabsorption • Symptomatic individuals with type 1 diabetes mellitus • Asymptomatic individuals 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	<ul style="list-style-type: none"> • Individuals with any of the following: <ul style="list-style-type: none"> ○ Persistent unexplained abdominal or gastrointestinal symptoms ○ Faltering growth ○ Prolonged fatigue ○ Unexpected weight loss ○ Severe or persistent mouth ulcers ○ Unexplained iron, vitamin B12, or folate deficiency ○ Type 1 diabetes, at diagnosis ○ Autoimmune thyroid disease, at diagnosis ○ Irritable bowel syndrome (in adults) • First-degree relatives of people with celiac disease • Consider serological testing for individuals with any of the following: <ul style="list-style-type: none"> ○ Metabolic bone disorder (reduced bone mineral density or osteomalacia) ○ Unexplained neurological symptoms (particularly peripheral neuropathy or ataxia) ○ Unexplained subfertility or recurrent miscarriage ○ Persistently raised liver enzymes with unknown cause ○ Dental enamel defects ○ Down's syndrome ○ Turner syndrome
North American Society for Pediatric Gastroenterology, Hepatology and Nutrition ³³	<ul style="list-style-type: none"> • Asymptomatic children ≥ 3 years of age with type 1 diabetes mellitus, autoimmune thyroiditis, Down syndrome, Turner syndrome, Williams syndrome, and selective IgA deficiency • Asymptomatic children ≥ 3 years of age 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	<ul style="list-style-type: none"> • Individuals with signs/symptoms of malabsorption • Individuals with unexplained iron-deficiency anemia unresponsive to iron supplementation • Individuals with dermatitis herpetiformis

Abbreviation: IgA=immunoglobulin A.

Table 2. Natural History of Celiac Disease

Author, year	Population Country N Age	Duration of followup	Definition of CD	Prevalence		Health outcomes	
				Classical CD	Non-classical CD (including screen-detected)	Classical CD	Non-classical 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 per 1000 person years (95% CI 5.4-16.1) After adjustment for age, gender, 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 IgA tTG antibody and positive IgA EmA	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 IgA EmA	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 IgA tTG antibody or IgA EmA	NA	1.1% EmA positive, 2.9% tTG positive	NA	Age- and sex-adjusted relative risk of overall mortality with positive IgA EmA: 0.78 (95% CI 0.52-1.18) Age- and sex-adjusted relative risk of overall mortality among positive IgA tTG: 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	
				Classical CD	Non-classical CD (including screen-detected)	Classical CD	Non-classical CD (including screen-detected)
Ludvigsson, 2009 ⁷⁴	Adults who underwent 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 in CD, 6.7 among those 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 IgA tTG antibody	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 Air Force Base N=9,133 Mean age 21 years	45 years	Positive IgA tTG antibody or IgA EmA	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: CD=celiac disease; CI=confidence interval; EmA=anti-endomysial antibody; HLA=human leukocyte antigen; IgA=immunoglobulin A; NA=not applicable; NR=not reported; OR=odds ratio; tTG=anti-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 tTG antibody tests associated with high sensitivity and specificity in populations not restricted to asymptomatic persons. Based on new studies, the pooled sensitivity in the systematic review was 92.8% (95% CI, 90.3% to 94.8%) and specificity 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 two studies of serological 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 a gluten-free diet associated with small improvements in gastrointestinal symptoms (less than 1 point on a 1 to 7 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 versus non-gluten-free diet in persons with screen-detected celiac disease.	-	High Non-U.S. setting	Imprecision	Poor

Abbreviations: CI=confidence interval; EmA=anti-endomysial antibody; tTG=anti-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.

Appendix A1. Search Strategies

- 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.

Appendix A1. Search Strategies

- 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

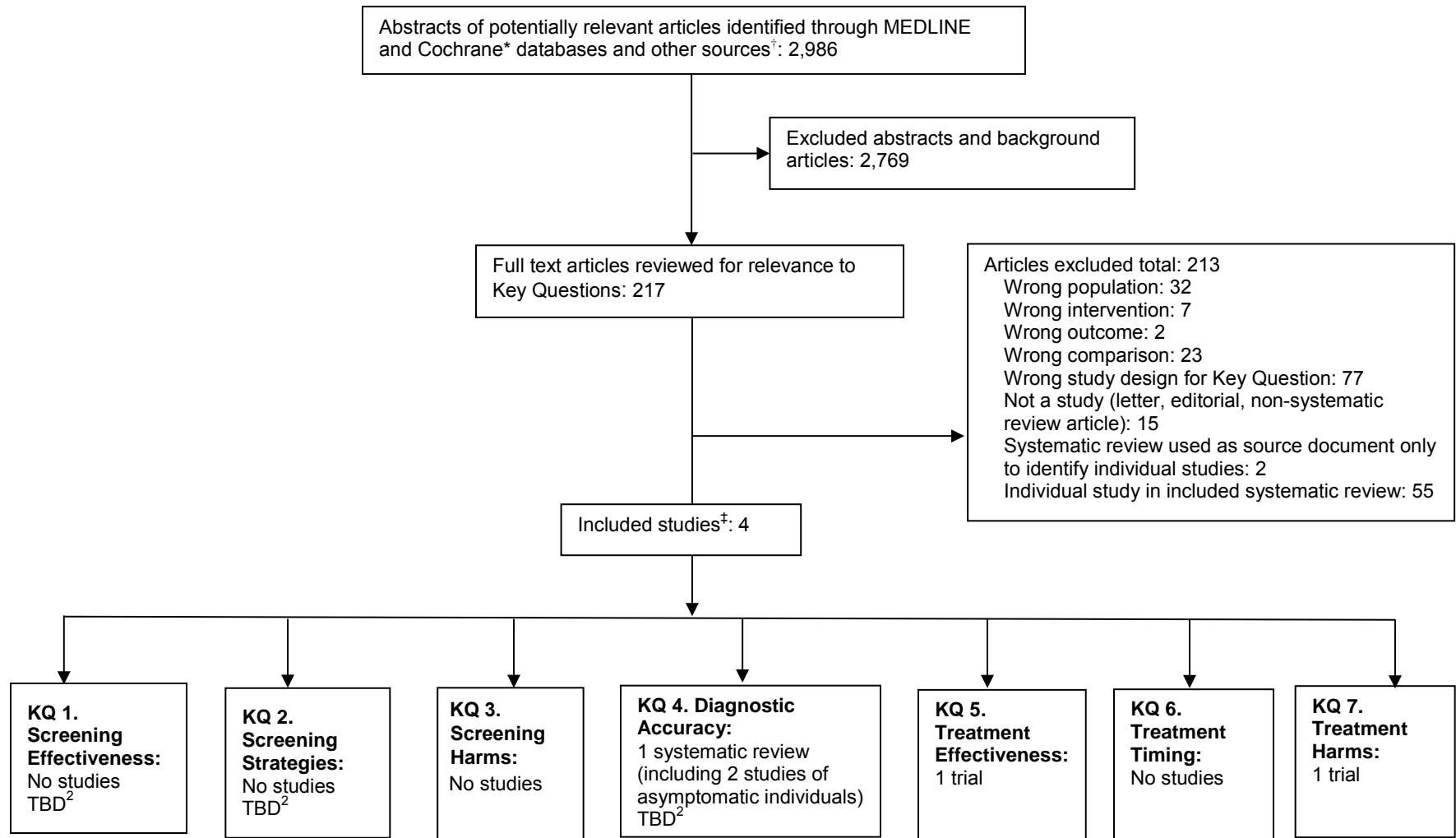
- 1 (celiac or coeliac).ti.
- 2 1 and gluten.mp.

Appendix A2. Inclusion and Exclusion Criteria

	Include	Exclude
Populations	<p>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)</p> <p>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)</p> <p>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)</p>	<p>KQs 1–3: Symptomatic persons seeking evaluation for potential celiac disease</p>
Interventions	<p>KQs 1, 2: Serologic screening (IgA tTG antibody or other commonly used tests)</p> <p>KQ 3: Serologic screening (IgA tTG antibody or other commonly used tests); diagnostic testing</p> <p>KQ 4: Serologic screening (IgA tTG antibody or other commonly used tests); questionnaires</p> <p>KQs 5–7: Gluten-free diet</p>	<p>KQ 4: Screening with biopsy only of patients with positive serology</p>
Comparators	<p>KQ 1: Screening vs. no screening</p> <p>KQ 2: Targeted vs. universal screening</p> <p>KQ 4: Endoscopy with biopsy</p> <p>KQ 5: Screen-detected treatment vs. no treatment</p> <p>KQ 6: Screen-detected celiac disease vs. disease detected after clinical diagnosis</p>	
Outcomes	<p>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</p> <p>KQ 3: Labeling, complications/harms from workup/biopsy, and overdiagnosis</p> <p>KQ 4: Sensitivity, specificity, positive and negative predictive values, area under the receiver operating curve, and other measures of diagnostic test accuracy</p> <p>KQ 7: Any harms of treatment</p>	<p>KQs 1, 2, 5, 6: Laboratory values for nutritional or other deficiencies</p>
Settings	<p>KQs 1–3: Primary care</p>	<p>KQs 1–3: Specialty clinics</p>
Study designs	<p>KQs 1–3, 7: Randomized, controlled trials; controlled observational studies; systematic reviews</p> <p>KQ 4: Studies evaluating diagnostic accuracy of serologic screening or questionnaires compared with intestinal biopsy; systematic reviews</p> <p>KQs 5, 6: Randomized, controlled trials; systematic reviews</p>	<p>KQ 4: Case-control studies</p>

Abbreviations: IgA=immunoglobulin A; KQ=key question; tTG=anti-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, systematic reviews, etc.

‡Studies may be included for more than one key question.

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 Nutr.* 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 Nutr.* 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, Leibold 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.
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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.
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- Farre C, Humbert P, Vilar P, et al. Serological markers and HLA-DQ2 haplotype among first-degree relatives of celiac patients. Catalanian 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.
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- 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.
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- Grainje 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 anti-gliadin 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.
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- 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 Gastrointest 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.
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- 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.
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- 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.
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- 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.
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- 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.
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- 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.
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- 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.

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- 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, Ekblom 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 reticulon 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.
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- 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.
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- 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.
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Appendix A4. Excluded Studies List

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- 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.
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Appendix A4. Excluded Studies List

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- 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.
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- 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.
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- 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.
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- 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.
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- 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.
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- 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.
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- 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.
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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.

Appendix A5. United States Preventive Services Quality Criteria for Rating Individual Studies

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).

Appendix A5. United States Preventive Services Quality Criteria for Rating Individual Studies

- 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

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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 for the diagnosis of celiac disease, including serological tests, HLA typing, video capsule endoscopy, and endoscopic duodenal biopsy.	Databases: PubMed, Embase, The Cochrane Library, and Web of Science Search dates: From 1990 to 2015 Additional data sources: Unpublished data were requested by the AHRQ-funded Scientific Resource Center and from manufacturers of all serological 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 the study 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 conducted in U.S., 3 in the U.K., 5 in the Middle East, 1 in India, and the rest in Continental Europe Race/ethnicity rarely described All studies included symptomatic patients or patients with risk factors or family history of celiac disease 6 studies were conducted in children and/or adolescents, and an additional 3 studies included a mixed population of children and adults

Appendix B1. Systematic Review of Diagnostic Accuracy Studies

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	<p>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)</p> <p>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)</p> <p>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)</p> <p>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)</p> <p>HLA typing No evidence</p> <p>Algorithms using one or more tests Insufficient evidence due to heterogeneity</p>	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 & Quality; CD, celiac disease; DGP, deaminated gliadin peptide; EmA, endomysial antibodies; HLA, Human Leukocyte Antigen; tTG, anti-tissue transglutaminase; U.K., United Kingdom; U.S., 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	IgA tTG, IgG tTG, IgA EMA, IgA AGA, and IgG AGA	Biopsy	University Hospital Iraq	NR	Mean age: 23.4 years; range 8 to 42 years	62	Marsh 3a-c: 11.3% (7/62)	Type 1 diabetic patients with no symptoms associated with celiac disease and no family history of celiac disease or thyroid disorders
Nevorál, 2014 ³⁷	Cross-sectional	IgA tTG and IgA EMA	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	IgA tTG: 71% IgG tTG: 57% IgA EmA: 71% IgA AGA: 57% IgG AGA: 57%	IgA tTG: 93% IgG tTG: 93% IgA EmA: 96% IgA AGA: 98% IgG AGA: 98%	NR	Fair
Nevorál, 2014 ³⁷	IgA tTG >10 ULN and positive EmA test: 67% Subgroups First-degree relatives (n=32): 70% Type 1 diabetes mellitus (n=40): 64%	IgA tTG >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, Anti-gliadin antibodies; AUROC, area under the receiver operating curve; EMA, anti-endomyseial antibodies; 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
Nevoal, 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	<p>A. Gluten diet (n=20) B. Gluten free diet (GFD) group (n=20)</p> <p>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.</p>	<p>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</p>	<p>Targeted screening (recruited relatives of celiac patients). Included EmA-positive adults (ages 18-75) who considered themselves asymptomatic (defined as an absence of: abdominal pain [>3 episodes over at least 3 months interfering with function], constipation [<3 bowel movements per week or difficulty during defecation], and diarrhea [≥ 3 loose stools/day], and extraintestinal symptoms such as joint pain, blistering rash or unexplained neurologic symptoms, and alarm symptoms including unexplained severe weight loss, vomiting, frequent or continuous fever, or rectal bleeding). Celiac disease was defined as the presence of positive EmA and gluten-dependent enteropathy. Excluded those with a previous diagnosis of celiac disease, age <18 years, evident clinical symptoms, dietary gluten restriction, severe contemporary illness or immunosuppressive medication, ongoing or planned pregnancy.</p>	<p>Screened: 3,031 at risk volunteers Eligible: 40 Enrolled: 40 Analyzed: 40 Withdrawals or loss to followup: None</p>

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	<p>Serology</p> <p>Celiac-related genotyping</p> <p>Gastrointestinal Symptoms Rating Scale (GSRS): 7-point Likert scale, higher score indicates more severe symptoms</p> <p>Psychological General Well-being (PGWB): 6-point Likert scale, higher score indicates better health-related quality of life</p> <p>Short-Form 36 (SF-36): 0-100, higher scores indicate better health-related quality of life</p> <p>Visual Analogue Scale (VAS): 0-100, higher scores indicate better subjective perception of health</p> <p>Laboratory parameters</p> <p>Bone mineral density</p> <p>Body composition</p> <p>Small bowel mucosal morphology and inflammation</p>	<p><u>Gastrointestinal symptoms after 1 year, difference in mean change (95% CI):</u></p> <p>GSRS Total -0.4 (-0.7 to -0.1), p=0.003, favors GFD</p> <p>GSRS Diarrhea -0.6 (-1.1 to 0.0), p=0.052, favors GFD</p> <p>GSRS Indigestion -0.7 (-1.1 to -0.2), p=0.006, favors GFD</p> <p>GSRS Constipation -0.1 (-0.5 to 0.3), p=0.325</p> <p>GSRS Abdominal pain -0.2 (-0.5 to 0.2), p=0.126</p> <p>GSRS Reflux -0.5 (-0.9 to -0.1), p=0.050, favors GFD</p> <p><u>Psychological general well-being, after 1 year, difference in mean change (95% CI):</u></p> <p>PGWB Anxiety 1.6 (0.4 to 2.8), p=0.025, favors GFD</p> <p>PGWB Depression 0.3 (-0.5 to 1.2), p=0.281</p> <p>PGWB Well-being 0.5 (-1.0 to 2.0), p=0.700</p> <p>PGWB Self-control 0.3 (-0.7 to 1.4), p=0.775</p> <p>PGWB General health 0.7 (-1.0 to 2.4), p=0.532</p> <p>PGWB Vitality 0.4 (-1.5 to 2.2), p=0.670</p> <p><u>Short-form 36, after 1 year, difference in mean change (95% CI):</u></p> <p>SF-36 Physical functioning -2.8 (-8.2 to 2.6), p=0.299</p> <p>SF-36 Role limitations due to physical problems 2.3 (-12.4 to 17), p= 0.749</p> <p>SF-36 Role limitations due to emotional problems 7.2 (-12.6 to 27), p=0.464</p> <p>SF-36 Vitality 6.0 (-4.3 to 16.4), p=0.245</p> <p>SF-36 Mental health 2.6 (-3.8 to 8.9), p=0.414</p> <p>SF-36 Social functioning -8.3 (-15.8 to -0.8), p=0.031, favors gluten group</p> <p>SF-36 Bodily pain 0.8 (-9.8 to 11.4), p=0.881</p> <p>SF-36 General health 2.8 (-7.1 to 12.7), p=0.568</p> <p>VAS: Improved in the GFD group (p=0.017)</p> <p><u>Laboratory parameters:</u></p> <p>Mean blood hemoglobin (SD), g/dL:</p> <p>A. Baseline 14.3 ± 1.4, Change after 1 year -0.2 ± 0.6</p> <p>B. Baseline 14.4 ± 1.6, Change after 1 year -0.2 ± 0.7</p> <p>Mean difference between groups 0.0 (95% CI -0.4 to 0.4), p=0.902</p> <p>Mean serum total iron (SD), micromol/L:</p> <p>A. Baseline 17.3 ± 5.7, Change after 1 year 2.8 ± 6.8</p> <p>B. Baseline 20.0 ± 8.6, Change after 1 year 0.3 ± 7.2</p> <p>Mean difference between groups -2.5 (95% CI -7.0 to 2.1), p=0.288</p>	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
		<p><u>Body composition:</u> Mean BMI (SD) kg/m²: 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 <u>BMD:</u> Mean lumbar spine (SD) g/cm²: 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/cm²: 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</p>				

Abbreviations: BMD, bone mineral density; BMI, body mass index; CI, confidence interval; EmA, Endomysial autoantibodies; GFD, gluten-free diet; GSRS, Gastrointestinal 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; 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