Specifications for Effective Health Care (EHC) Clinician Research Summary

Page Size: 8.5 x 11 inches

Margins: 1/2 of an inch on all four sides (.5 inches)

Ink colors: ***Clinician Research Summary:*** Use Pantone 295 (blue) for banner and headings. Use Pantone 370 (green) for bullets, rules, and other accents. Make body text black.

In special cases, where a full-color figure is required to convey essential information, use a 5-color treatment as follows: equivalents of full process color plus the primary Pantone color.

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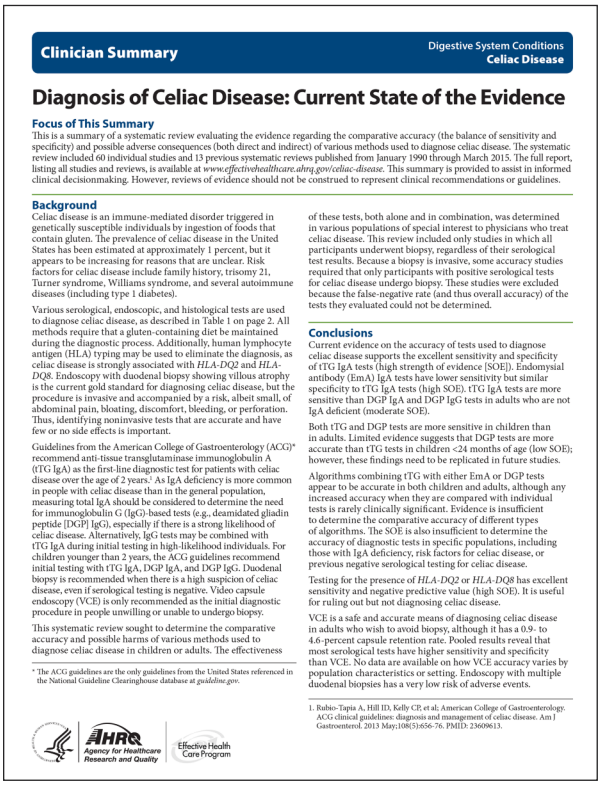
Sample product



Clinician Summary

Digestive System Conditions
Celiac Disease

Diagnosis of Celiac Disease: Current State of the Evidence

Focus of This Summary

This is a summary of a systematic review evaluating the evidence regarding the comparative accuracy (the balance of sensitivity and specificity) and possible adverse consequences (both direct and indirect) of various methods used to diagnose celiac disease. The systematic review included 60 individual studies and 13 previous systematic reviews published from January 1990 through March 2015. The full report, listing all studies and reviews, is available at *www.effectivehealthcare.ahrq.gov/celiac-disease.* This summary is provided to assist in informed clinical decisionmaking. However, reviews of evidence should not be construed to represent clinical recommendations or guidelines.

Background

Celiac disease is an immune-mediated disorder triggered in genetically susceptible individuals by ingestion of foods that contain gluten. The prevalence of celiac disease in the United States has been estimated at approximately 1 percent, but it appears to be increasing for reasons that are unclear. Risk factors for celiac disease include family history, trisomy 21, Turner syndrome, Williams syndrome, and several autoimmune diseases (including type 1 diabetes).

Various serological, endoscopic, and histological tests are used to diagnose celiac disease, as described in Table 1 on page 2. All methods require that a gluten-containing diet be maintained during the diagnostic process. Additionally, human lymphocyte antigen (HLA) typing may be used to eliminate the diagnosis, as celiac disease is strongly associated with *HLA-DQ2* and *HLA-DQ8*. Endoscopy with duodenal biopsy showing villous atrophy is the current gold standard for diagnosing celiac disease, but the procedure is invasive and accompanied by a risk, albeit small, of abdominal pain, bloating, discomfort, bleeding, or perforation. Thus, identifying noninvasive tests that are accurate and have few or no side effects is important.

Guidelines from the American College of Gastroenterology (ACG)* recommend anti-tissue transglutaminase immunoglobulin A (tTG IgA) as the first-line diagnostic test for patients with celiac disease over the age of 2 years.[1] As IgA deficiency is more common in people with celiac disease than in the general population, measuring total IgA should be considered to determine the need for immunoglobulin G (IgG)-based tests (e.g., deamidated gliadin peptide [DGP] IgG), especially if there is a strong likelihood of celiac disease. Alternatively, IgG tests may be combined with tTG IgA during initial testing in high-likelihood individuals. For children younger than 2 years, the ACG guidelines recommend initial testing with tTG IgA, DGP IgA, and DGP IgG. Duodenal biopsy is recommended when there is a high suspicion of celiac disease, even if serological testing is negative. Video capsule endoscopy (VCE) is only recommended as the initial diagnostic procedure in people unwilling or unable to undergo biopsy.

This systematic review sought to determine the comparative accuracy and possible harms of various methods used to diagnose celiac disease in children or adults. The effectiveness of these tests, both alone and in combination, was determined in various populations of special interest to physicians who treat celiac disease. This review included only studies in which all participants underwent biopsy, regardless of their serological test results. Because a biopsy is invasive, some accuracy studies required that only participants with positive serological tests for celiac disease undergo biopsy. These studies were excluded because the false-negative rate (and thus overall accuracy) of the tests they evaluated could not be determined.

Conclusions

Current evidence on the accuracy of tests used to diagnose celiac disease supports the excellent sensitivity and specificity of tTG IgA tests (high strength of evidence [SOE]). Endomysial antibody (EmA) IgA tests have lower sensitivity but similar specificity to tTG IgA tests (high SOE). tTG IgA tests are more sensitive than DGP IgA and DGP IgG tests in adults who are not IgA deficient (moderate SOE).

Both tTG and DGP tests are more sensitive in children than in adults. Limited evidence suggests that DGP tests are more accurate than tTG tests in children <24 months of age (low SOE); however, these findings need to be replicated in future studies.

Algorithms combining tTG with either EmA or DGP tests appear to be accurate in both children and adults, although any increased accuracy when they are compared with individual tests is rarely clinically significant. Evidence is insufficient to determine the comparative accuracy of different types of algorithms. The SOE is also insufficient to determine the accuracy of diagnostic tests in specific populations, including those with IgA deficiency, risk factors for celiac disease, or previous negative serological testing for celiac disease.

Testing for the presence of *HLA-DQ2* or *HLA-DQ8* has excellent sensitivity and negative predictive value (high SOE). It is useful for ruling out but not diagnosing celiac disease.

VCE is a safe and accurate means of diagnosing celiac disease in adults who wish to avoid biopsy, although it has a 0.9- to 4.6-percent capsule retention rate. Pooled results reveal that most serological tests have higher sensitivity and specificity than VCE. No data are available on how VCE accuracy varies by population characteristics or setting. Endoscopy with multiple duodenal biopsies has a very low risk of adverse events.

* The ACG guidelines are the only guidelines from the United States referenced in the National Guideline Clearinghouse database at *guideline.gov.*

1. Rubio-Tapia A, Hill ID, Kelly CP, et al; American College of Gastroenterology. ACG clinical guidelines: diagnosis and management of celiac disease. Am J Gastroenterol. 2013 May;108(5):656-76. PMID: 23609613.

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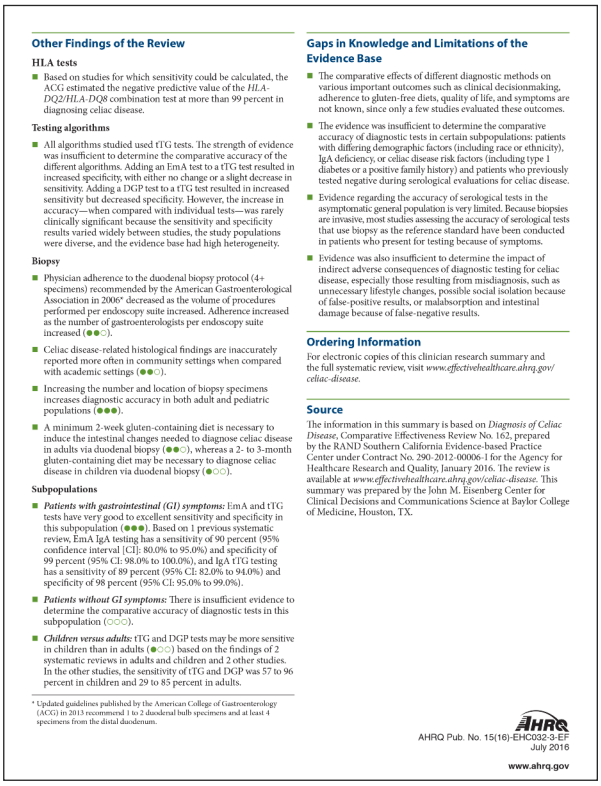

Other Findings of the Review

HLA tests

- Based on studies for which sensitivity could be calculated, the ACG estimated the negative predictive value of the *HLA-DQ2/HLA-DQ8* combination test at more than 99 percent in diagnosing celiac disease.

Testing algorithms

- All algorithms studied used tTG tests. The strength of evidence was insufficient to determine the comparative accuracy of the different algorithms. Adding an EmA test to a tTG test resulted in increased specificity, with either no change or a slight decrease in sensitivity. Adding a DGP test to a tTG test resulted in increased sensitivity but decreased specificity. However, the increase in accuracy—when compared with individual tests—was rarely clinically significant because the sensitivity and specificity results varied widely between studies, the study populations were diverse, and the evidence base had high heterogeneity.

Biopsy

- Physician adherence to the duodenal biopsy protocol (4+ specimens) recommended by the American Gastroenterological Association in 2006* decreased as the volume of procedures performed per endoscopy suite increased. Adherence increased as the number of gastroenterologists per endoscopy suite increased (●●○).
- Celiac disease-related histological findings are inaccurately reported more often in community settings when compared with academic settings (●●○).
- Increasing the number and location of biopsy specimens increases diagnostic accuracy in both adult and pediatric populations (●●●).
- A minimum 2-week gluten-containing diet is necessary to induce the intestinal changes needed to diagnose celiac disease in adults via duodenal biopsy (●●○), whereas a 2- to 3-month gluten-containing diet may be necessary to diagnose celiac disease in children via duodenal biopsy (●○○).

Subpopulations

- ***Patients with gastrointestinal (GI) symptoms:*** EmA and tTG tests have very good to excellent sensitivity and specificity in this subpopulation (●●●). Based on 1 previous systematic review, EmA IgA testing has a sensitivity of 90 percent (95% confidence interval [CI]: 80.0% to 95.0%) and specificity of 99 percent (95% CI: 98.0% to 100.0%), and IgA tTG testing has a sensitivity of 89 percent (95% CI: 82.0% to 94.0%) and specificity of 98 percent (95% CI: 95.0% to 99.0%).
- ***Patients without GI symptoms:*** There is insufficient evidence to determine the comparative accuracy of diagnostic tests in this subpopulation (○○○).
- ***Children versus adults:*** tTG and DGP tests may be more sensitive in children than in adults (●○○) based on the findings of 2 systematic reviews in adults and children and 2 other studies. In the other studies, the sensitivity of tTG and DGP was 57 to 96 percent in children and 29 to 85 percent in adults.

* Updated guidelines published by the American College of Gastroenterology (ACG) in 2013 recommend 1 to 2 duodenal bulb specimens and at least 4 specimens from the distal duodenum.

Gaps in Knowledge and Limitations of the Evidence Base

- The comparative effects of different diagnostic methods on various important outcomes such as clinical decisionmaking, adherence to gluten-free diets, quality of life, and symptoms are not known, since only a few studies evaluated these outcomes.
- The evidence was insufficient to determine the comparative accuracy of diagnostic tests in certain subpopulations: patients with differing demographic factors (including race or ethnicity), IgA deficiency, or celiac disease risk factors (including type 1 diabetes or a positive family history) and patients who previously tested negative during serological evaluations for celiac disease.
- Evidence regarding the accuracy of serological tests in the asymptomatic general population is very limited. Because biopsies are invasive, most studies assessing the accuracy of serological tests that use biopsy as the reference standard have been conducted in patients who present for testing because of symptoms.
- Evidence was also insufficient to determine the impact of indirect adverse consequences of diagnostic testing for celiac disease, especially those resulting from misdiagnosis, such as unnecessary lifestyle changes, possible social isolation because of false-positive results, or malabsorption and intestinal damage because of false-negative results.

Ordering Information

For electronic copies of this clinician research summary and the full systematic review, visit *www.effectivehealthcare.ahrq.gov/celiac-disease.*

Source

The information in this summary is based on *Diagnosis of Celiac Disease*, Comparative Effectiveness Review No. 162, prepared by the RAND Southern California Evidence-based Practice Center under Contract No. 290-2012-00006-I for the Agency for Healthcare Research and Quality, January 2016. The review is available at *www.effectivehealthcare.ahrq.gov/celiac-disease.* This summary was prepared by the John M. Eisenberg Center for Clinical Decisions and Communications Science at Baylor College of Medicine, Houston, TX.

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Specifications for Effective Health Care (EHC) Clinician Research Summary

Design Elements: ***EHC banner:*** The EHC banner with rounded corners should be used at the top of page 1. The banner includes the topic name and subject area. The banner should be flush with the top, left, and right margins at 1/2 inch. The banner must not be stretched, cropped, or modified in any way. The banner should be Pantone 295 (blue) with white lettering.

Sample banner

Clinician Summary

Digestive System Conditions
Celiac Disease

Charts and tables: Charts and tables should be in shaded boxes with rounded corners.

Photos: The only photos used are images of the corresponding EHC consumer booklet front cover. The cover prints as a gray-scale image.

Columns: After the introductory text, which spans the page width, text will appear in two columns. The only exception to this are the "Source" and "For More Information" pages which may be one column depending on fit and design. Charts, figures, and other visuals may be one or two columns as required for best layout.

Page numbers: Page numbers should appear on each page, except for the first page, in a size equal to the body text. Page numbers are not needed if the summary is front and back only.

Specifications for Effective Health Care (EHC) Clinician Research Summary

Fonts: Use the fonts below. Due to their complexity, charts and graphs can have text smaller than 11-point, but no smaller than 8 point.

Title: 20-point Myriad Pro Bold.

Body text: 11-point Minion Pro with 13-point leading.

Level 1 heads: 14-point Myriad Pro Bold.

Level 2 heads: 11-point Myriad Pro Bold.

Level 3 heads: 11-point Myriad Pro Italic.

Run-in heads: 11-point Minion Pro Bold.

Bullets: Square.

Hyphenation: Should be turned off.

Sample fonts and sizes

Sample Title is 20-point Myriad Pro Bold

Head Level 1 is 14-point Myriad Pro Bold

Head Level 2 is 11-point Myriad Pro Bold

Head Level 3 is 11-point Myriad Pro Italic

Body text is 11-point Minion Pro with 13-point leading. It should be flush left, ragged right, with no hyphenation.

- This is a sample of bulleted text with a square bullet. It should be flush left, ragged right, with no hyphenation. The text size is 11-point Minion Pro with 13-point leading.

Run-in heads. This is a sample of a run-in head. The run-in head is 11-point Minion Pro Bold.

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Branding:

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Front cover branding logo

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All AHRQ publications being printed for distribution from the AHRQ Clearinghouse must bear an AHRQ publication number and a date. These items normally appear at the bottom of cover four or on the last page of fact sheets and marketing materials. The AHRQ logo and publication number may be flush right or left depending on the design. The AHRQ editor will provide publication numbers to contractors. See sample below of flush left back cover.

Back cover logo

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For print-ready proofs to go to the Government Printing Office (GPO), provide AHRQ source files in Adobe InDesign. Include fonts, logos, and any picture files (TIFs, EPS, or JPGs) with the source files.

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GPO also requires that a completed Form 952 accompany print files. This form is downloadable from the GPO Web site at www.gpo.gov.

August 2016