NATIONAL GUIDELINE CLEARINGHOUSE™ (NGC) GUIDELINE SYNTHESIS

DIAGNOSIS AND MANAGEMENT OF CELIAC DISEASE

Guidelines

1. **American Gastroenterological Association Institute (AGA)**. AGA Institute medical position statement on the diagnosis and management of celiac disease. Gastroenterology 2006 Dec;131(6):1977-80. PubMed
2. **National Institutes of Health (NIH) Consensus Development Panel on Celiac Disease**. Celiac disease. Bethesda (MD): U.S. Department of Health and Human Services (DHHS); 2004 Aug 9. 15 p.
3. **World Gastroenterology Organisation (WGO-OMGE)**. WGO-OMGE practice guideline: celiac disease. Paris (France): World Gastroenterology Organisation (WGO-OMGE); 2005 Feb. 18 p.

INTRODUCTION

A direct comparison of the American Gastroenterological Association (AGA) Institute, the National Institutes of Health (NIH), and the World Gastroenterology Organisation (WGO-OMGE) recommendations for screening, diagnosis and management of celiac disease is provided in the tables below.

The guidelines are similar in scope, providing recommendations for the topics addressed above, as well information on the epidemiology and prevalence of celiac disease. Epidemiology and prevalence of celiac disease, however, are beyond the scope of this synthesis. NIH and WGO-OMGE also provide recommendations for future research. In formulating their recommendations AGA reviewed the conclusions drawn by NIH during the consensus development panel. While WGO-OMGE does not explicitly cite the NIH guideline as a reference, they do include it in a list of other celiac disease guidelines.

The tables below provide a side-by-side comparison of key attributes of each guideline, including specific interventions and practices that are addressed. The language used in these tables, particularly that which is used in Tables 4 and 5 is in most cases taken verbatim from the original guidelines:

- Table 1 provides a quick-view glance at the primary interventions considered by each group.
- Table 2 provides a comparison of the overall scope of both guidelines.
- Table 3 provides a comparison of the methodology employed and documented by both groups in developing their guidelines.
- Table 4 provides a more detailed comparison of the specific recommendations offered by each group for the topics under consideration in this synthesis, including:
    - Diagnosis and Assessment

A summary discussion of the areas of agreement and differences among the guidelines is presented following the content comparison tables.

Abbreviations:

- AGA, antigliadin antibody
- AGA Institute, American Gastroenterological Association Institute
- CD, celiac disease
- ELISA, enzyme-linked immunosorbent assay
- EMA, antiendomysial antibody
- GFD, gluten-free diet
- NIH, National Institutes of Health
- tTGA, tissue transglutaminase antibody
- WGO-OMGE, World Gastroenterology Organisation

TABLE 1: COMPARISON OF INTERVENTIONS AND PRACTICES CONSIDERED *("✓" indicates topic is addressed)*			
	AGA (2006)	**NIH (2004)**	**WGO (2005)**
Diagnosis			
Serologic Testing			
• IgA endomysial antibody (EMA)	✓	✓	✓
• IgA tissue transglutaminase antibodies (tTG)	✓	✓	✓
• Antigliadin	✓but not	✓but not	✓but not

antibody (IgA AGA; IgG AGA)	recommended	recommended	recommended
Endoscopy	✓	✓	✓
Intestinal biopsy	✓	✓	✓
HLA-DQ2 and DQ8 testing to exclude the diagnosis of celiac disease	✓	✓	
Management			
Gluten-free diet (GFD)	✓	✓	✓
Education	✓	✓	✓
Dietitian consultation	✓	✓	✓
Follow-Up/Persistence of Symptoms	✓	✓	✓

TABLE 2: COMPARISON OF SCOPE AND CONTENT	
Objective and Scope	
AGA (2006)	• To provide recommendations to gastroenterologists and primary care practitioners on the diagnosis and management of celiac disease • To suggest preferred approaches to specific medical issues or problems

NIH (2004)	• To improve awareness, diagnosis, and management of celiac disease
	• To examine the current state of knowledge regarding celiac disease and to identify directions for future research. Specifically, the following key questions were addressed:
	  • How is celiac disease diagnosed?
	  • How prevalent is celiac disease?
	  • What are the manifestations and long-term consequences

	of celiac disease? • Who should be tested for celiac disease? • What is the management of celiac disease? • What are the recommendations for future research on celiac disease and related conditions?
WGO-OMGE (2005)	To provide practice guidelines for the diagnosis and management of celiac disease
Target Population	
AGA (2006)	Adult patients with suspected celiac disease **Note:** The major focus is on adults, although some data from studies on children are also included for completeness.
NIH (2004)	Patients with confirmed or suspected celiac disease
WGO-OMGE (2005)	Patients with celiac disease or suspected celiac disease
Intended Users	
AGA (2006)	Dietitians Physicians
NIH (2004)	Dietitians Health Care Providers Nurses Physicians
WGO-OMGE (2005)	Dietitians Health Care Providers Nurses Physician Assistants Physicians

TABLE 3: COMPARISON OF METHODOLOGY	
Methods Used to Collect/Select the Evidence	
AGA (2006)	*Searches of Electronic Databases* *Described Process*: The literature search is current and includes outcomes not covered in a prior report. Citations identified by the search strategy underwent multilevel screening by 2 independent reviewers using predetermined forms detailing the inclusion and exclusion criteria. The reference list for this review is extensive and has been shortened to meet length requirements. The guideline developers reference sections of the Agency for Healthcare Research and Quality report, and the updated list in its entirety is available online (http://www.ahrq.gov/downloads/pub/evidence/pdf/celiac/celiac.pdf) and (http://www.ahrq.gov/clinic).
NIH (2004)	*Searches of Electronic Databases* *Described Process*: The Agency for Healthcare Research and Quality (AHRQ) supported the National Institutes of Health (NIH) Consensus Development Conference on Celiac Disease through its Evidence-based Practice Center (EPC) program. Under contract to the AHRQ, the University of Ottawa EPC developed the systematic review and analysis that served as a reference for discussion at the conference. The National Library of Medicine in collaboration with the University of Ottawa EPC conducted the literature search. A series of systematic reviews on five areas of celiac disease (CD) were completed: 1. Sensitivity and specificity of serological tests 2. Prevalence and incidence of CD 3. CD-associated lymphoma 4. Consequences of testing for CD 5. Interventions for the promotion and monitoring of adherence to a gluten-free diet (GFD) Staff at the National Library of Medicine performed a series of searches in support of the literature review of celiac disease. Searches were run in the MEDLINE® (1966 to Oct 2003) and EMBASE (1974 to Dec 2003) databases for each of the five objectives and their respective sub-objectives separately.

	Furthermore, for the 4th and 5th objectives, PsycINFO (1840 forward), AGRICOLA (1970 forward), CAB (1972 forward), and Sociological Abstracts (1963 forward) database searches were run in December 2003. Study selection for each objective was performed using three levels of screening with predetermined increasingly more strict criteria to ensure that all relevant articles were captured. Following a calibration exercise, two reviewers independently screened all studies using a Web-based system that allowed automatic identification of review disagreements. These disagreements were resolved by consensus. For each CD objective, a detailed and standardized data abstraction form was developed. For each objective, data abstraction was conducted by one reviewer and verified by another. The extracted data was further verified by one of the principal investigators. Quality assessments were performed using specific instruments for each of the included study types. The following is available: • Rostom A, Dubé C, Cranney A, et al. Celiac Disease. Summary, Evidence Report/Technology Assessment: Number 104. Rockville (MD): Agency for Healthcare Research and Quality; AHRQ Publication Number 04-E029-1; 2004 Jun. Electronic copies available from the Agency for Healthcare Research and Quality (AHRQ) Web site.
WGO-OMGE (2005)	*Hand-searches of Published Literature (Primary Sources)* *Searches of Electronic Databases* *Described Process*: **World Gastroenterology Organization's (WGO's) Graded Evidence System** WGO's Grading Evidence System is built to help National Societies of Gastroenterology and all those interested in the practice and research of gastroenterology, keep track of the literature in topics covered by WGO Guidelines. Evidence is classified into three categories: • Systematic reviews, consensus statements, meta-analyses, evidence-based practice guidelines • Clinical trials

- Other reading

The following journals are scanned for new evidence:

- Gastroenterology
- Annals of Internal Medicine
- Hepatology
- GUT
- Journal of Hepatology
- Alim. pharmacology & therapeutics
- American Journal of Gastroenterology
- Inflammatory Bowel Disease
- Gastrointestinal Endoscopy
- J. of Pediatric Gastroenterology & Nutrition
- Digestion
- Scandinavian Journal of Gastroenterology
- Eur. J. of Gastroenterology and Hep.
- Digestive Diseases and Sciences
- Endoscopy
- J. of Gastroenterology and Hepatology
- Digestive Surgery
- Digestive Diseases

Plus a selection from the general journals:

- New England Journal of Medicine
- JAMA
- Lancet
- BMJ
- Nature
- Science

Coverage

Graded Evidence is an iterative process—and for that reason need not be so concerned with searching Medline, Embase and Biosis for example. All top gastrointestinal (GI) journals are covered by both Medline and Embase and in single one-off complex searches unique citations in one or the other are often due either to differences in database currency or differences in coverage of less important journals. In addition to cost issues, the generous republishing and copyright policies of the US National Library of Medicine (NLM) make Medline the preferred choice.

Search Strategies

Search strategies for each topic are based on a combination of controlled access and free text terms. The strategies aim for "precision" rather than "sensitivity." Busy gastroenterologists probably prefer very precise search strategies in top GI journals and

	thus make sure every major article is found. The WGO Graded Evidence works along the lines of PUBMED Medline "Clinical queries" features. Precise searches only find relevant information. Indexing errors may still be responsible for irrelevant or duplicate records. Case studies and animal studies are not usually included. **Finding Evidence** True evidence-based searches require a deeper understanding of databases and search strategies not necessary for our purpose. WGO Global Guidelines are not systematic reviews. The WGO Library adheres to the Cochrane Collaboration's views that a searcher has to work through a hierarchy of evidence as follows. • Cochrane Collaboration Systematic Reviews • DARE Systematic Reviews • Randomized Clinical Trials (e.g., in the Cochrane Controlled Clinical Trials Database) As you move down the hierarchy you are more likely to find "opinion" instead of evidence.
Methods Used to Assess the Quality and Strength of the Evidence	
AGA (2006)	*Expert Consensus*
NIH (2004)	*Expert Consensus*
WGO-OMGE (2005)	*Expert Consensus*
Methods Used to Analyze the Evidence	
AGA (2006)	*Review* *Described Process*: Included articles were assessed for quality using a design-specific instrument. The obtained data were extracted and statistically pooled if clinically and statistically appropriate. If statistical pooling was not possible, a qualitative description of the studies is presented.
NIH (2004)	*Systematic Review* *Described Process*:

	The data obtained from this review fell into several broad categories, which correspond in large part to the individual study objectives. Data for the sensitivity and specificity of each serological marker was considered separately, and studies were further divided according to the age group of the study population. Attempts were made to identify, explain, and minimize clinical and statistical heterogeneity in the included studies. A Pearson's Chi Square with n-1 degrees of freedom, where n represents the number of included studies in an analysis, was calculated to assess statistical heterogeneity. Pooled estimates were only calculated, if clinically and statistically appropriate. In situations where pooling was not performed, a qualitative systematic review was conducted. To produce clinically useful pooled statistics, a weighted mean of the overall sensitivity and specificity from the included studies was calculated, along with 95-percent confidence intervals (CIs). The pooled estimates for the sensitivity and specificity were compared with a summary receiver operating characteristic (ROC) curve, calculated for the same group of studies as a second check of the estimates.
WGO-OMGE (2005)	• *Review* • *Review of Published Meta-Analyses*
	Methods Used to Formulate the Recommendations
AGA (2006)	*Expert Consensus* *Described Process:* The recommendations are based upon the interpretation and assimilation of scientifically valid research, derived from a comprehensive review of published literature. Ideally, the intent is to provide evidence based upon prospective, randomized placebo-controlled trials; however, when this is not possible the use of experts' consensus may occur.
NIH (2004)	*Expert Consensus (Consensus Development Conference)* *Described Process*: The National Institutes of Health (NIH) convened a Consensus Development Conference on Celiac Disease on June 28-30, 2004. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the Office of Medical Applications of Research (OMAR) of the NIH were the primary sponsors of this meeting. The U.S. Food and Drug Administration, the U.S. Department of Agriculture, the National Institute of Child Health and Human Development, the National Cancer Institute, and the National Institute of Allergy and

	Infectious Diseases were the cosponsors. This two-and-a-half-day conference examined the current state of knowledge regarding celiac disease and identified directions for future research. During the first day-and-a-half of the conference, experts presented the latest celiac disease research findings to an independent panel. After weighing this scientific evidence, the panel drafted a statement that addressed the key questions.
WGO-OMGE (2005)	Not stated
Outcomes	
AGA (2006)	• Sensitivity and specificity of diagnostic tests • Effectiveness of gluten-free diet • Risk of mortality and lymphoma
NIH (2004)	• Sensitivity and specificity of serological tests for celiac disease • Value of standardized pathology criteria for the diagnosis of celiac disease • Symptom resolution following adoption of a gluten-free diet • Value of genetic marker testing (human leukocyte antigen [HLA] haplotypes) in the diagnosis of celiac disease • Prevalence rates of celiac disease and identification of high risk groups who may benefit from screening • Disease manifestations, long-term consequences, and complications • Morbidity and mortality associated with celiac disease
WGO-OMGE (2005)	• Sensitivity and specificity of diagnostic tests • Symptom resolution • Morbidity and mortality
Financial Disclosures/Conflicts of Interest	
AGA (2006)	Martin F. Kagnoff is supported by National Institutes of Health grants DK35108 and DK58960 and a grant from the William K. Warren Foundation.
NIH (2004)	Not stated
WGO-OMGE	Not stated

(2005)	

TABLE 4: COMPARISON OF RECOMMENDATIONS FOR THE DIAGNOSIS AND TREATMENT OF CELIAC DISEASE	
DIAGNOSIS AND ASSESSMENT	
Definition	
AGA (2006)	**Celiac disease** is a permanent intolerance to gluten, a term that is broadly used to describe the storage proteins in wheat, rye, and barley. Celiac disease is characterized by a chronic inflammatory state of the proximal small intestinal mucosa, which can impair digestion and absorption of macronutrients and micronutrients and results in increased net secretion of water and solute. **Common Definitions of Celiac Disease:** **Classic celiac disease** is the most commonly described form. It describes patients with the classic features of intestinal malabsorption who have fully developed gluten-induced villous atrophy and other classic histologic features. These patients present because of gastrointestinal symptoms. **Atypical celiac disease** appears to be the most common form. These patients generally have little to no gastrointestinal symptoms but come to medical attention because of other reasons such as iron deficiency, osteoporosis, short stature, or infertility. These patients generally have fully developed gluten-induced villous atrophy. Because these patients are "symptomatic" from the gastrointestinal perspective, a large number go undiagnosed. **Silent celiac disease** refers to asymptomatic patients who are discovered to have gluten-induced villous atrophy. They are discovered after serologic screening or perhaps during endoscopy and biopsy for another reason. These patients are clinically silent in that they do not manifest any clear gastrointestinal symptoms or associated atypical features of celiac disease such as iron deficiency or osteoporosis. **Latent celiac disease** represents patients with a previous diagnosis of celiac disease that responded to a gluten-free diet (GFD) and who retain a normal mucosal histology or manifest only an increase in intraepithelial lymphocytes. Latent celiac disease can also represent patients with currently normal intestinal mucosa on a

	gluten-containing diet who will subsequently develop celiac disease. **Refractory celiac disease** represents patients with true celiac disease (i.e., not a misdiagnosis) who do not or no longer respond to a GFD. Some of these patients develop complications such as ulcerative jejunoileitis or enteropathy-associated T-cell lymphoma.
NIH (2004)	**Celiac disease** is an immune-mediated disorder that affects primarily the gastrointestinal tract. It is characterized by chronic inflammation of the small intestinal mucosa that may result in atrophy of intestinal villi, malabsorption, and a variety of clinical manifestations, which may begin in either childhood or adult life. Intestinal symptoms can include diarrhea, abdominal cramping, pain, and distention, and untreated celiac disease may lead to vitamin and mineral deficiencies, osteoporosis, and other extraintestinal problems. There is a strong genetic predisposition to celiac disease, with the major risk attributed to the specific genetic markers known as HLA-DQ2 and HLA-DQ8 that are present in affected individuals. Dietary proteins present in wheat, barley, and rye, commonly known as glutens, interact with these HLA molecules to activate an abnormal mucosal immune response and induce tissue damage. There is an existing classification of patients with putative subphenotypes. Whether these subphenotypes are clinically useful remains to be determined. These include the following: **Classical celiac disease** is dominated by symptoms and sequelae of gastrointestinal malabsorption. The diagnosis is established by serological testing, biopsy evidence of villous atrophy, and improvement of symptoms on a gluten-free diet. **Celiac disease with atypical symptoms** is characterized by few or no gastrointestinal symptoms, and extraintestinal manifestations predominate. Recognition of atypical features of celiac disease is responsible for much of the increased prevalence, and now may be the most common presentation. As with classical celiac disease, the diagnosis is established by serologic testing, biopsy evidence of villous atrophy, and improvement of symptoms on a gluten-free diet. **Silent celiac disease** refers to individuals who are asymptomatic but have a positive serologic test and villous atrophy on biopsy. These individuals usually are detected via screening of high-risk individuals, or villous atrophy occasionally may be detected by endoscopy and biopsy conducted for another reason. **Latent celiac disease** is defined by a positive serology but no villous atrophy on biopsy. These individuals are asymptomatic, but later may develop symptoms and/or histologic changes.

WGO-OMGE (2005)	**Celiac disease**: An enteropathy affecting the (small) intestine in genetically predisposed children and adults, precipitated by the ingestion of gluten-containing foods (e.g., wheat, rye, and barley). It is also referred to as celiac sprue, gluten-sensitive enteropathy, or nontropical sprue. The clinical classification of celiac disease (CD) has undergone a change; today, most experts agree with the following classification: **Classical** Mostly gastrointestinal symptoms **Atypical** Mostly nongastrointestinal symptoms — usually monosymptomatic or oligosymptomatic **Silent** No symptoms despite the presence of a characteristic intestinal lesion
Screening/Assessment	
AGA (2006)	It is the position of the American Gastroenterological Association (AGA) Institute that testing for celiac disease should be considered in symptomatic individuals who are at particularly high risk. These include those with unexplained iron deficiency anemia (IDA), a premature onset of osteoporosis, Down syndrome, unexplained elevations in liver transaminase levels, primary biliary cirrhosis, and autoimmune hepatitis. Situations in which testing for celiac disease should be selectively considered during the medical evaluation, especially if symptoms that could be the result of celiac disease are present, include type 1 diabetes mellitus, autoimmune thyroid disease, Sjögren's syndrome, unexplained recurrent fetal loss, unexplained delayed puberty, selective IgA deficiency, irritable bowel syndrome, Turner's syndrome, peripheral neuropathy, cerebellar ataxia, and recurrent migraine, as well as children with short stature and first- and second-degree relatives of patients with celiac disease (see the original guideline document for a more detailed description of each of the high risk populations).
NIH (2004)	**Who should be tested for celiac disease?** Individuals with gastrointestinal symptoms, including chronic diarrhea, malabsorption, weight loss, and abdominal distention, should be tested for celiac disease. Because celiac disease is a multisystem disorder, physicians should be aware of other conditions for which celiac disease testing should be considered. Individuals without other explanations for signs and symptoms such as persistent elevations of transaminases, short stature, delayed puberty, iron-deficiency anemia, recurrent fetal loss, and infertility should be tested.

	Other conditions for which celiac disease testing may be considered include irritable bowel syndrome, persistent aphthous stomatitis, autoimmune diseases, peripheral neuropathy, cerebellar ataxia, and dental enamel hypoplasia. Although individuals with celiac disease often present with osteoporosis, data do not indicate a significantly increased prevalence of celiac disease in the general population of people with osteoporosis. There are many other associated systemic symptoms that are not specific to celiac disease but for which celiac disease testing might be considered. There are a number of populations at higher risk for celiac disease. These include individuals with type 1 diabetes mellitus, other autoimmune endocrinopathies, first- and second-degree relatives of individuals with celiac disease, and individuals with Turner syndrome. Individuals and physicians should be aware of the increased prevalence of celiac disease in these groups. Symptomatic individuals in these populations should be tested for celiac disease; for example, an individual with type 1 diabetes mellitus and unexplained hypoglycemia merits testing. Because current data do not indicate a clear outcome benefit for early detection and treatment of asymptomatic individuals in these groups, routine screening cannot be recommended at this time, but individual discussions regarding the benefits and consequences of testing are warranted. Other populations at increased risk for celiac disease include individuals with Down syndrome and Williams syndrome. When individuals in these groups are unable to describe symptoms, screening may be appropriate and should be offered. At this time, there are insufficient data to recommend screening of the general population for celiac disease. For individuals who have been placed on a gluten-free diet without an appropriate diagnostic evaluation, testing should follow a gluten challenge. For those who decline to undergo a gluten challenge, the absence of DQ2 and DQ8 by HLA typing may help exclude the diagnosis. Resolution of symptoms on a gluten-free diet is not sufficient to diagnose celiac disease; however, there are no adverse nutritional outcomes associated with a carefully planned gluten-free diet.
WGO-OMGE (2005)	**<u>Diagnosis of Celiac Disease (CD)</u>** **Key Symptoms** *Adults: Gastrointestinal Symptoms* • Chronic diarrhea (most common symptom) • Weight loss • Anemia • Abdominal distension

- Lassitude and malaise

Children: Gastrointestinal Symptoms

- Failure to thrive, weight loss, down-shift of weight or height centile, short stature
- Vomiting
- Diarrhea
- Recurrent abdominal pain
- Muscle wasting
- Irritable bowel
- Hypoproteinemia
- Irritability and unhappiness

Adults and Children: Nongastrointestinal Symptoms

- Iron deficiency/anemia
- Dermatitis herpetiformis
- Peripheral neuropathy
- Folic acid deficiency
- Reduced bone density
- Unexplained infertility

Consider CD in Cases of:

- Unexplained folic acid, iron, or B12 deficiency
- Reduced serum albumin
- Unexplained hypertransaminasemia
- Osteoporosis and osteomalacia
- Recurrent abdominal pain or bloating
- Skin rashes

Management of Celiac Disease

Initial approach:

- Advise serological screening for first-degree and second-degree relatives

Screening for Celiac Disease

The current view is that there is not enough evidence to support a decision to carry out mass screening of the general population, nor is there enough evidence to assess the risks of undetected CD.

NGC Note: Refer to the original guideline document for a discussion of possible differential diagnoses and populations at high-risk of celiac disease.

Diagnostic Testing	
AGA (2006)	Diagnostic tests should be performed before the initiation of gluten restriction begins. Positive serologic test results may resolve and histologic findings may improve with the removal of gluten from the diet. The initial detection of possible celiac disease is probably best obtained by the use of a simple and accurate serologic test: the IgA tTGA. ***Serologic Testing*** The diagnostic approach to detecting celiac disease has undergone important changes in recent years. Serologic tests, particularly the IgA antiendomysial antibody (EMA) and the IgA tTGA, have become a relatively sensitive and specific way to initially detect celiac disease. The IgA tTGA is both sensitive and specific for celiac disease and supplants the use of gliadin antibody testing as the preferred means of serologic detection. Overall, many studies demonstrate a specificity of IgA tTGA greater than 95% and a sensitivity in the range of 90% to 96%. The EMA detected by an indirect immunofluorescence assay is more time consuming and operator dependent than the tTGA. It has a slightly lower and variable sensitivity but an excellent specificity (99.6%). IgA antigliadin antibody by enzyme-linked immunosorbent assay predates the previously described serologic tests, but its diagnostic performance compared with IgA tTGA and IgA EMA is not attractive. The prevalence of IgA deficiency in celiac disease is sufficiently low, such that the routine measurement of serum IgA levels along with IgA EMA or tTGA is not warranted as a first step toward diagnosis unless IgA deficiency is strongly suspected. In cases of selective IgA deficiency, either the IgG EMA and/or IgG tTGA have excellent sensitivity and specificity, although those IgG-based tests are markedly less sensitive and specific than the IgA-based tests in those with normal levels of IgA. Measurement of the serum IgA level is an appropriate next step in individuals with a negative IgA EMA or IgA tTGA in whom celiac disease is still suspected. If celiac disease is strongly suspected despite negative serologic test results, one can test for the presence of the disease-associated HLA alleles and, if present, proceed to small intestinal mucosal biopsy. Alternatively, it is reasonable to proceed directly to upper intestinal endoscopy and small bowel biopsy if the signs and symptoms that suggested celiac disease would otherwise warrant those procedures. **Conclusion.** In the primary care setting, the IgA tTGA is the most efficient single serologic test for the detection of celiac disease. Evidence indicates that the additional inclusion of IgG antigliadin antibody and IgA antigliadin antibody is not warranted. ***Intestinal Biopsy*** Positive serologic test results are supportive of the diagnosis of

	celiac disease. Distal duodenal biopsy specimens demonstrating characteristic histologic changes in the small intestinal mucosa, which includes a spectrum of change from total to partial villous atrophy, and crypt lengthening with an increase in lamina propria and intraepithelial lymphocytes, remain the gold standard for establishing the diagnosis of celiac disease. An increase in intraepithelial lymphocytes without other mucosal changes may represent latent celiac disease or a part of the spectrum of gluten-sensitive enteropathy but should not be considered diagnostic of celiac disease. It is important to take multiple (ideally 6) biopsy specimens and best to obtain these from the second part of the duodenum or beyond because mucosal changes can be patchy or Brunner's glands or peptic changes may hamper histopathologic examination if biopsy specimens are obtained from the more proximal duodenum. Gluten challenge and a repeat biopsy are no longer required to establish the diagnosis of celiac disease in patients whose initial small intestinal biopsy specimen has the characteristic histologic appearance and in whom an objective response to a GFD is obtained. However, a gluten challenge with a subsequent biopsy does have a role in establishing the diagnosis in select clinical settings (e.g., in those with a high suspicion for celiac disease and a negative serologic test result and who started on a GFD without biopsy confirmation of the disease). It is crucial that the dietary status of the patient at the time of biopsy be taken into account. Patients should undergo biopsy promptly after obtaining a positive serologic test result and should be instructed not to avoid gluten until after biopsy specimens are obtained. A gluten-reduced diet may reduce the severity of the lesion and impact pathologic interpretation. How long gluten must be reintroduced before biopsy specimens are taken can vary among individuals already on a GFD. A 4-week challenge with sufficient gluten to reproduce the symptoms is adequate in most. However, some patients may have very delayed responses, and it can take up to several years for relapse to occur. Reaching a definitive diagnosis can be difficult in those with minimal histologic findings, in those with a negative serologic test result, or if the disease is patchy or an insufficient number or poorly oriented biopsy specimens were taken. There are other disease entities that can resemble celiac disease histologically. Most of these entities are either rare in the developed world, are suggested by the clinical history, or have distinguishing histologic findings on careful review of the biopsy samples. Endoscopy provides a ready opportunity to examine the duodenal mucosa visually and to obtain a sufficient number of biopsy specimens. However, the visual examination of the small bowel mucosa is not entirely sensitive for identifying villous atrophy, although endoscopists should be aware of the visual appearance of villous atrophy. Endoscopists should not regard the absence of visual endoscopic features of celiac disease as sufficient to rule out the diagnosis.

	Use of HLA-DQ2 and -DQ8 to Exclude the Diagnosis of Celiac Disease Approximately 40% of the general population in the United States have either the HLA class II heterodimer HLADQ2 or HLA-DQ8, which reflects the presence of the DQ alleles DQA1*05 and DQB1*02 (DQ2) or DQA1*03 and DQB1*0302 (DQ8). However, almost all patients with celiac disease have either DQ2 (~95% of patients with celiac disease) or DQ8 (~5% of patients with celiac disease). A very small number of patients with celiac disease have been noted to have only DQA1*O5 or DQB1*02, the latter usually being associated with HLA-DR7 heterozygosity or homozygosity. Because virtually all patients with celiac disease have the celiac disease-associated alleles mentioned previously at the DQA1 and DQB1 loci, the absence of these alleles provides a negative predictive value for the disease of close to 100% (i.e., if individuals lack the relevant disease-associated alleles, celiac disease is virtually excluded). HLA testing for the relevant DQ alleles can be a useful adjunct in an exclusionary sense when the diagnosis based on other tests is not clear. When using HLA testing in the context of disease susceptibility in families, one must have the resources available to provide genetic counseling.
NIH (2004)	**How is Celiac Disease Diagnosed?** The single most important step in diagnosing celiac disease is to first consider the disorder by recognizing its myriad clinical features. There is no one test that can definitively diagnose or exclude celiac disease in every individual. Just as there is a clinical spectrum of celiac disease, there is also a continuum of laboratory and histopathologic results. The combination of clinical and laboratory features may result in a diagnosis of celiac disease. All diagnostic tests need to be performed while the patient is on a gluten-containing diet. The first step in pursuing a diagnosis of celiac disease is a serologic test. Based on very high sensitivities and specificities, the best available tests are the IgA antihuman tissue transglutaminase (TTG) and IgA endomysial antibody immunofluorescence (EMA) tests that appear to have equivalent diagnostic accuracy (TTG is the specific protein that is identified by the IgA-EMA). Antigliadin antibody (AGA) tests are no longer routinely recommended because of their lower sensitivity and specificity. Serologic testing for celiac disease in children less than 5 years of age may be less reliable and requires further study. Biopsies of the proximal small bowel are indicated in individuals with a positive celiac disease antibody test, except those with biopsy-proven dermatitis herpetiformis. Endoscopic evaluation without biopsies is inadequate to confirm or exclude a diagnosis since endoscopic findings are not sufficiently sensitive for celiac

	disease. Multiple biopsies should be obtained because the histologic changes may be focal. Biopsies should be obtained from the second portion of the duodenum or beyond. The pathology report should specify the degree of crypt hyperplasia and villous atrophy as well as assess the number of intraepithelial lymphocytes. Some degree of villous atrophy is considered necessary to confirm a diagnosis of celiac disease. The finding of intraepithelial lymphocytes with crypt hyperplasia without villous blunting is less definitive. Standardization of the pathology reports in celiac disease is desirable, using published criteria such as modified Marsh criteria (1999). Communication between the pathologist and the individual's physician is encouraged to help correlate the biopsy findings with laboratory results and clinical features. Second opinions on biopsy interpretation may be sought when biopsy results are discordant with serologic markers or clinical findings. With concordant positive serology and biopsy results, a presumptive diagnosis of celiac disease can be made. Definitive diagnosis is confirmed when symptoms resolve subsequently with a gluten-free diet. A demonstration of normalized histology following a gluten-free diet is no longer required for a definitive diagnosis of celiac disease. In an individual with suggestive symptoms and a negative serology test, three scenarios are possible. First, the individual may have selective IgA deficiency. If an IgA deficiency is identified, an IgG-TTG or IgG-EMA test should be performed. Second, the serologic test may be a "false negative," and if this is suspected the test could be repeated, an alternative serologic test could be conducted, and/or a small intestinal biopsy could be performed. Third, the patient may not have celiac disease. When the diagnosis of celiac disease is uncertain because of indeterminate results, testing for certain genetic markers (HLA haplotypes) can stratify individuals to high or low risk for celiac disease. Greater than 97 percent of celiac disease individuals have the DQ2 and/or DQ8 marker, compared to about 40 percent of the general population. Therefore, an individual negative for DQ2 or DQ8 is extremely unlikely to have celiac disease (high negative predictive value). Patient preferences should be elicited in developing recommendations in the setting of a positive celiac disease serology and normal biopsy results. A single best approach cannot be prescribed. Choices include additional small bowel biopsies, periodic monitoring with celiac disease serology tests, or a trial of gluten-free diet.
WGO-OMGE (2005)	**<u>Diagnostic Tests</u>** Only endoscopy with biopsy of the small intestine plus a positive CD

serology provide a definitive diagnosis. This is the gold standard. (See the algorithm in the original guideline document on diagnosis of celiac disease.)

Role of Endoscopy for Suspicion of Celiac Disease

Although endoscopy may provide an indication for intestinal biopsy, it may not be sufficiently sensitive to detect all manifestations of CD in a population.

The characteristic findings of an endoscopy include:

- Scalloped folds, fissures and mosaic pattern
- Flattened folds
- Smaller size and or disappearing of folds with maximum insufflation

Intestinal Biopsy

Intestinal biopsies together with a positive serology represent the gold standard for diagnosing celiac disease.

Multiple biopsies are taken from the second or third part of the duodenum. Endoscopy has become the most convenient method of obtaining biopsies of the small-intestinal mucosa. Suction biopsy (Crosby capsule) provides the best samples.

Histological Characteristics of Celiac Enteropathy

CD affects the mucosa of the proximal small intestine, with damage gradually decreasing in severity towards the distal small intestine, although in severe cases the lesions can extend to the ileum. The degree of proximal damage varies greatly depending on the severity of the disease. The proximal damage may be very mild in "silent" cases, with little or no abnormality detectable histologically in the mid-jejunum. Abnormalities in the gastric and rectal mucosa may be observed in some cases.

Occasionally, the lesion in the duodenum/upper jejunum can be patchy, which may justify a second biopsy immediately in selected patients with positive endomysial antibody (EMA). However this is only warranted if all three samples of the first biopsy show a normal histology.

Use of Serum Antibodies to Diagnose Celiac Disease

- IgA endomysial antibody (IgA EMA; highest diagnostic accuracy)
- IgA tissue transglutaminase antibody (IgA tTG)
- IgA antigliadin antibody (IgA AGA)

- IgG antigliadin antibody (IgG AGA)

Serologic studies for celiac disease can be divided into two groups, based on the target antigens:

- Anti-tTG antibody tests
- Antigliadin antibody tests

IgA EMA - IgA endomysial antibodies bind to endomysium, the connective tissue around smooth muscle, producing a characteristic staining pattern that is visualized by indirect immunofluorescence.

The test result is reported simply as positive or negative, since even low titers of serum IgA endomysial antibodies are specific for CD. The target antigen has been identified as tissue transglutaminase (tTG or transglutaminase 2).

IgA endomysial antibody testing is moderately sensitive and highly specific for untreated (active) CD.

Anti-tissue transglutaminase antibodies (IgA tTG). The antigen against which antiendomysial antibodies are directed is tTG. Anti-tTG antibodies are highly sensitive and specific for the diagnosis of CD.

Enzyme-linked immunosorbent assay (ELISA) tests for IgA anti-tTG antibodies are now widely available and are easier to perform, less observer-dependent and less costly than the immunofluorescence assay used to detect IgA endomysial antibodies. The diagnostic accuracy of IgA anti-tTG immunoassays has been improved further by the use of human tTG in place of the nonhuman tTG preparations used in earlier immunoassay kits.

Antigliadin antibody assays (IgA AGA and IgG AGA). Gliadins are the major proteins of the wheat storage proteins collectively termed gluten.

Purified gliadin is readily available and is used as the antigen for ELISA tests to detect serum antigliadin antibodies.

Serum antigliadin antibody levels are frequently elevated in untreated CD, and antigliadin assays have been used for some years as a diagnostic aid.

Although these tests demonstrate moderate sensitivity and specificity, with the IgA tests being superior, their positive predictive value in the general population is relatively poor.

AGA tests are no longer routinely recommended, because of their

lower sensitivity and specificity.

The Global Aspect

The diagnosis of CD can be made with different diagnostic technologies in different parts of the world, depending on the available resources, but the specificity and validity of the results may vary when tools poorer than those of the "gold standard" are used.

Depending on available resources, diagnostic options can be cascaded from a highly resourced setting in which the above gold standard can be used — endoscopy followed by small-bowel biopsy and specific serology for confirmation or case finding — to a situation in which very few resources are available and only the minimum can be done.

If biopsy is not available, "serology only" remains a feasible method for diagnosing CD, also because serological tests are cheaper than endoscopy and biopsy and their statistical value is very similar.

In the absence of a biopsy, the criteria are:

- The presence of auto-antibodies
- Gluten dependency of the auto-antibody titer
- Clinical symptoms, when present
- Improvements in symptoms and reduction in the anti-tTG antibody titer on a gluten-free diet
- In children, catch-up growth, when applicable

The easiest and cheapest serological test would be the dot ELISA. Once a bedside IgA anti tTG test becomes available and sufficiently sensitive and specific, it would be ideal for low-income regions.

If a geographic area has very limited resources, clinical aspects become the most important diagnostic tool. A rice-based or corn-based GFD is the final and vital step in confirming a diagnosis of CD.

Although endoscopy is a very useful tool for detecting CD, it cannot be relied on as a single diagnostic procedure. The presence of markers of mucosal atrophy may be highly suggestive of CD be in places where the disease is common, but in other areas of the world there may be several differential diagnoses — for example, tropical sprue, malnutrition, heavy-chain disease, etc.).

Nevertheless, the procedure is very helpful when markers are elevated in the course of endoscopies ordered for other reasons. Then the endoscopist must be alert and proceed to intestinal biopsy.

MANAGEMENT	
AGA (2006)	Treatment of celiac disease requires a strict, lifelong adherence to a gluten free diet (GFD). This is also the case for patients with dermatitis herpetiformis. Clinicians need to ensure that patients have adequate education, motivation, and support to achieve this diet. Consultation with an experienced dietician, referral to a support group, and clinical follow-ups for compliance are recommended. Treatment of nutritional deficiency states (e.g., iron, folate, vitamin B_{12}) is essential, and a determination of bone mineral density to assess for osteoporosis is recommended. ***Promoting Adherence to a GFD*** Changes in dietary habits are difficult to maintain, and there are many barriers to continued compliance with a GFD. Improved knowledge of celiac disease, the GFD, gluten-containing food products, and outcomes of untreated celiac disease would likely improve compliance. Membership in a local celiac society provides patients with celiac disease with improved knowledge regarding their disease, the intricacies of the GFD, and also emotional and social support opportunities. ***Expected Benefits of a GFD*** Compliance with a GFD is likely protective against the development of non-Hodgkin's lymphoma in celiac disease and dermatitis herpetiformis. There is compelling evidence that treatment of symptomatic celiac disease results in substantial improvement in nutritional parameters. The treatment of celiac disease with a GFD can result in improvements in bone mineral density, with the greatest improvements appearing in the first years of the GFD. Treatment with a GFD for at least 12 months can result in increased body weight, body mass index, fat mass, bone mass, triceps skin fold thickness, and nutritional and biochemical status including iron absorption. Patients adhering to a strict GFD usually consume fewer calories than noncompliers but show a trend toward greater improvements in measurements of body composition. The benefits of a GFD on short-term outcomes in diabetic patients with celiac disease are inconclusive. They suggest that nutritional parameters can improve but no convincing change in diabetic control has been demonstrated, although insulin requirements often increase.
NIH (2004)	Treatment for celiac disease should begin only after a complete diagnostic evaluation including serology and biopsy. The management of celiac disease is a gluten-free diet for life. A gluten-free diet is defined as one that excludes wheat, rye, and barley. These dietary grains contain the peptides or glutens known to cause celiac disease. Even small quantities of gluten may be

	harmful. Oats appear to be safe for use by most individuals with celiac disease, but their practical inclusion in a gluten-free diet is limited by potential contamination with gluten during processing. The strict definition of a gluten-free diet remains controversial due to the lack of an accurate method to detect gluten in food products and the lack of scientific evidence for what constitutes a safe amount of gluten ingestion. The following are six key elements in the management of individuals affected by celiac disease: **C**onsultation with a skilled dietitian **E**ducation about the disease **L**ifelong adherence to a gluten-free diet **I**dentification and treatment of nutritional deficiencies **A**ccess to an advocacy group **C**ontinuous long-term follow-up by a multidisciplinary team Learning about celiac disease and how to identify gluten-containing products is associated with improved self-management. Participation in an advocacy group is also an effective means of promoting adherence to a gluten-free diet and may provide emotional and social support. Health care providers should consider and treat vitamin and mineral deficiencies, including iron, calcium, phosphorus, folate, B_{12}, and fat-soluble vitamins. Individuals with newly diagnosed celiac disease should undergo screening for osteoporosis given the higher prevalence in this population. It is important to have a team-based approach to management. In addition to treatment by a physician and participation in a local advocacy group, consultation with a skilled dietitian is essential.
WGO-OMGE (2005)	**Management** The current treatment for CD is a strictly gluten-free diet for life. In the gluten-free diet, wheat, barley, and rye are avoided. Oats are not toxic in > 95% of patients with CD or dermatitis herpetiformis, but there is a small subgroup (< 5%) for whom oats are not safe. Additionally, there is a reluctance in some countries to advise liberal use of oats because of the difficulty in guaranteeing that commercially available oats will be free of contamination with other grains. Rice and corn can be part of a GFD.

Initial approach:

- Prescribe a "natural" gluten-free diet
- Refer to a dietician and/or support group (see web sites listed below)
- Screen for iron and folate deficiency
- Advise bone-density tests (in some cases)
- Advise vitamin D and calcium supplementation if the patient is osteoporotic
- Advise serological screening for first-degree and second-degree relatives

Most patients have a rapid clinical response to a gluten-free diet (within 2 weeks), although the rate of response varies. Patients who are extremely ill may require hospital admission, repletion of fluids and electrolytes, intravenous alimentation, and, occasionally, steroids. Patients should be encouraged to eat natural high-iron and high-folate foods, especially if a deficiency in these minerals is documented.

Patients should also have a consultation with a dietician who is knowledgeable about gluten-free diets. However, not all dieticians are familiar with the intricacies of a gluten-free diet, and for this reason local or national support groups provide most of the required information.

For adults, quality of life is improved on a gluten-free diet, even in those whose disease was detected by screening. Children on a gluten-free diet reported a quality of life comparable to that of a reference population. Adolescents have difficulty with dietary compliance.

(Refer to Table 5 in the original guideline document for foods allowed in a gluten-free diet)

The gluten-free diet

The most effective treatment is a rigorous gluten-free-diet (GFD) for life. This means no wheat, rye, or barley. Oats — provided they are pure and not contaminated with other grains (even minimal amounts of wheat, rye or barley) — are safe to eat in > 95% of cases.

Plain meat, fish, rice, corn, fruits, and vegetables do not contain gluten. Examples of foods that are safe to eat and those that are not can be found online. Useful online CD information sites are listed in sections 8 and 9.

A gluten-free diet is low in fiber. Patients should be advised to eat a high-fiber diet supplemented with whole-grain rice, maize, potatoes

	and ample vegetables. Correct any dietary deficiencies such as iron, folic acid, calcium and (very rarely) B_{12} deficiency.
Follow-Up/Persistence of Symptoms	
AGA (2006)	**Promoting Adherence to a GFD** Follow-up is necessary to confirm the diagnosis by an objective response to a GFD and to detect and manage noncompliance. Patients with celiac disease should be evaluated at regular intervals by a health care team including a physician and a dietician. These visits can be used to assess, by history, a patient's compliance with a GFD and to reinforce the importance of such compliance. Beyond this, there are no clear guidelines as to the optimal means to monitor adherence to a GFD. In general, monitoring adherence to a GFD with serologies (i.e., tTGA or EMA) is sensitive for major but not for minor transient dietary indiscretions. In children, histologic improvement on a GFD appears to occur quickly, while in adults the small intestinal mucosa heals more slowly and less completely. Monitoring adherence by clinic visits and serologic testing appears to be a reasonable approach in children. In adults, this approach is also reasonable with the understanding that a negative serologic test result does not necessarily mean improvement beyond severe subtotal or total villous atrophy. **Nonresponsive Celiac Disease** Patients with known celiac disease can continue to have or can redevelop symptoms despite being on a GFD. These symptoms may be due to incompletely healed celiac disease, an associated condition, a complication, or a second unrelated diagnosis. Persistent or intermittent symptoms due to known or inadvertent ingestion of gluten are commonly reported. If gluten ingestion is not suggested by direct review of the dietary history or positive serologic test result, then a careful search should be undertaken for other entities such as microscopic colitis, pancreatic exocrine insufficiency, bacterial overgrowth, and disaccharidase deficiency. Intestinal lymphoma, small bowel strictures, or true refractory sprue should be considered in the absence of these and in persistently febrile or very ill patients. Refractory sprue is a rare entity with a high morbidity and mortality and is defined as continued or recurrent malabsorption and diarrhea associated with persisting moderate or severe villous atrophy despite adherence to a strict GFD. The evaluation of these patients should include a careful evaluation for coexistent T-cell lymphomas. The optimal therapy for celiac sprue is not known but frequently includes immunosuppression.

NIH (2004)	The complications of celiac disease typically occur after many years of disease and usually are observed in adults. Refractory celiac disease refers to persistence of symptoms and intestinal inflammation despite a gluten-free diet. This may occur in the context of ulcerative jejunitis, or it may be an early manifestation of intestinal lymphoma. **<u>What is the Management of Celiac Disease?</u>** Following initial diagnosis and treatment, individuals should return for periodic visits with the physician and dietitian to assess symptoms and dietary adherence and monitor for complications. In children, this includes evaluation of growth and development. During these visits, health care providers can reinforce the benefits of adhering to a strict gluten-free diet for life. Repeat serologic testing may be used to assess response to treatment but is unproven. These tests may take a prolonged time (up to 1 year) to normalize, especially in adults, and may not correlate with improved histology. Persistent elevated serological levels may suggest lack of adherence to a gluten-free diet or unintended gluten ingestion. Individuals who do not respond to a gluten-free diet require reevaluation. No established approach exists to screen for complications of celiac disease including lymphoma and adenocarcinoma of the small bowel.
WGO-OMGE (2005)	**Persistence of Symptoms** A common difficulty with the GFD is the presence of occult gluten in processed foods and/or medicines (although this is rare). The persistence of symptoms is almost always caused by continued ingestion of gluten. Reasons for persistence of symptoms: • (Inadvertent) gluten ingestion (this is the most common reason) • Wrong diagnosis • Lactose or fructose intolerance • Other food intolerances • Pancreatic insufficiency • Microscopic colitis • Bacterial overgrowth • Collagenous colitis or collagenous sprue • Irritable bowel syndrome • Ulcerative jejunitis • Enteropathy-associated T-cell lymphoma • Refractory CD

	The last three can be regarded as complications of long-lasting CD. **Refractory Celiac Disease** The diagnosis of refractory CD is considered in patients with features of CD who have persistent symptoms, villous atrophy, and failure to respond to a gluten-free diet. This may occur at presentation, or after an initial response to a gluten-free diet. Refractory CD is considered to be a form of low-grade intraepithelial lymphoma, revealed by severe malabsorption that is not responsive to a gluten-free diet. This diagnosis must be considered particularly in celiac disease patients who are diagnosed over the age of 50.

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WGO-OMGE (2005)	Not stated

TABLE 5: BENEFITS AND HARMS
Benefits

AGA (2006)	**Overall Benefits** Appropriate diagnosis and management of celiac disease **Specific Benefits** • Compliance with a gluten-free diet (GFD) is likely protective against the development of non-Hodgkin's lymphoma in celiac disease and dermatitis herpetiformis. • There is compelling evidence that treatment of symptomatic celiac disease results in substantial improvement in nutritional parameters. The treatment of celiac disease with a GFD can result in improvements in bone mineral density, with the greatest improvements appearing in the first years of the GFD. Treatment with a GFD for at least 12 months can result in increased body weight, body mass index, fat mass, bone mass, triceps skin fold thickness, and nutritional and biochemical status including iron absorption. Patients adhering to a strict GFD usually consume fewer calories than noncompliers but show a trend toward greater improvements in measurements of body composition. • Making the diagnosis at a young age, educating patients and parents, and utilizing a multidisciplinary approach to patient management and follow-up would be expected to improve compliance and patient outcomes.
NIH (2004)	Improved awareness, diagnosis, and management of celiac disease
WGO-OMGE (2005)	Improved diagnosis and management of celiac disease to reduce disease-associated morbidity and improve quality of life
Harms	
AGA (2006)	Not stated
NIH (2004)	False positive or false negative serological tests requiring additional investigative procedures
WGO-OMGE (2005)	False positive and false negative diagnostic tests

GUIDELINE CONTENT COMPARISON

The American Gastroenterological Association Institute (AGA Institute), National Institutes of Health (NIH), and the World Gastroenterology Organisation (WGO-OMGE) present recommendations for the screening, diagnosis, and management of celiac disease.

Each guideline develops a working definition for celiac disease along with classifications of celiac disease in order to clarify the spectrum of small intestinal mucosal injury and to list the intestinal and extraintestinal symptoms.

All three guidelines have a similar scope, each addressing screening, diagnosis, and management of celiac disease. All three discuss the immune response that occurs in patients with celiac disease and its prevalence in the general population. AGA and NIH suggest early mechanisms and initiating steps that may lead to celiac disease such as early introduction of cereals to infants, but this is beyond the scope of this synthesis.

Guideline Development Methodology

The NIH and AGA guidelines present their recommendations in a narrative format; each with an accompanying evidence report/technical review (see the "Availability of Companion Documents" field in the individual AGA and NIH summaries) that provides explicit reasoning and referenced citations. WGO-OMGE presents its recommendations in a narrative format with bullet points, but does not provide explicit reasoning or referenced citations for its recommendations.

The NIH guideline utilizes a systematic review that was developed by the University of Ottawa Evidence-based Practice Center under contract with the Agency for Healthcare Research and Quality (AHRQ). This NIH consensus development conference statement is referenced in the AGA guideline and is included in a list of other celiac disease guidelines by WGO-OMGE.

All three groups performed searches of electronic databases. WGO-OMGE also performed hand-searches of published literature (primary sources). WGO-OMGE provides a general list of journals scanned, a search strategy, and some evidence classification used for all of their guidelines, but no specific search terms or inclusion/exclusion criteria for this specific guideline. NIH provides the names of databases that were searched, as well as the dates for which the searches were performed. Specific search terms and inclusion/exclusion criteria are not provided. AGA states that their literature search is current and includes outcomes not provided in the AHRQ/NIH report. Although inclusion and exclusion criteria are mentioned, specific criteria used, along with search terms and search strategies are not provided.

NIH and AGA state that their data was extracted and statistically pooled if clinically and statistically appropriate. If statistical pooling was not possible, NIH indicates that a qualitative systematic review was conducted. AGA did not conduct a systematic review if statistical pooling was not possible, but instead provided a qualitative description of the studies presented. Their intent was to provide evidence based upon prospective, randomized, placebo-controlled trials, but when this was not possible the use of experts' consensus was utilized. WGO-OMGE states that they reviewed 42 meta-analyses, systematic reviews, and practice guidelines; 11 clinical trials; and 56 other readings.

In terms of methods used to formulate the recommendations, NIH used expert consensus from a consensus development conference, AGA used expert consensus, and WGO-OMGE does not specifically state how their recommendations were formulated. None of the guideline developers employ rating schemes for the strength of the evidence or the strength of the recommendations.

Both NIH and AGA provide reference lists and both groups cite the supporting evidence in their technical reviews rather than linking them directly to the recommendation statements. WGO-OMGE does not provide supporting references but lists guidelines, websites, and articles for further reading.

AGA presents potential conflicts of interest.

Comparison of Recommendations Between the AGA, NIH and WGO-OMGE Guidelines	
Diagnosis	
Screening/Assessment	
AGA (2006)	• Suggests testing for celiac disease should be considered in symptomatic individuals who are at particularly high risk.
NIH (2004)	• Recommends that symptomatic individuals in high risk populations or those with specific gastrointestinal symptoms should be tested for celiac disease. • Cites insufficient data to recommend screening of the general population for celiac disease.
WGO-OMGE (2005)	• Recommends screening of first- and second-degree relatives of patients with CD, as well as screening of individuals with selected signs/symptoms • Cites that there is not enough evidence to support a decision to carry out mass screening of the general population, nor is there enough evidence to assess the risks of undetected CD.
Diagnostic Testing	
AGA (2006)	• Recommends serologic testing (particularly IgA tTGA), intestinal biopsy, and use of HLA-DQ2 and -DQ8 to exclude the diagnosis of celiac disease

NIH (2004)	• Suggests there is no one test that can definitively diagnose or exclude celiac disease in every individual. • Recommends serologic testing (particularly IgA TTG and IgA EMA), biopsies of the proximal small bowel, and testing for genetic markers (HLA haplotypes) • Cites that a definitive diagnosis is confirmed when symptoms resolve subsequently with a gluten-free diet
WGO-OMGE (2005)	• Recommends endoscopy with biopsy of the small intestine plus a positive celiac disease (CD) serology (particularly IgA EMA and Anti-tTG) to provide a definitive diagnosis. • Recommends a rice based or corn-based gluten free diet as the final and vital step in confirming a diagnosis of CD in geographic areas with limited resources.
Management	
AGA (2006)	• Recommends a strict, lifelong adherence to a gluten free diet (GFD) with patient education, clinical follow-up, treatment of nutritional deficiencies, and referral to support group or consultation with a dietician when indicated. • Recommends immunosuppression for refractory sprue
NIH (2004)	• Recommends a gluten-free diet for life that includes consultation with a dietician, patient education, identification and treatment of nutritional deficiencies, access to an advocacy group, and long-term follow-up
WGO-OMGE (2005)	• Recommends a rigorous gluten-free-diet (GFD) for life that includes referral to a dietician and/or support group, correction of any dietary deficiencies (such as iron, folic acid, calcium and B_{12} deficiency).

Areas of Agreement

Screening/Assessment

AGA, NIH, and WGO-OMGE are in general agreement regarding the lack of evidence to support screening the general population for celiac disease. Although WGO-OMGE recounts the five world health organization (WHO) criteria that should justify general screening, the guideline falls short of making such a recommendation, noting a lack of evidence to support the decision. All three groups also recommend screening for celiac disease among high risk populations and discuss the populations at higher risk for celiac disease, considering also the

associated diseases and conditions (see the original guideline documents for discussion of these high-risk populations).

Diagnostic Testing

All three guidelines are in agreement that serologic testing combined with intestinal biopsy are the "gold standard" for establishing a diagnosis of celiac disease, and that testing should be performed while on a gluten-containing diet. All three also agree that the best serologic tests are the tTG antibody tests, rather than the previously used antigliadin antibody (AGA) tests. AGA and NIH both agree that using HLA-DQ2 and DQ8 testing can exclude the presence of celiac disease. Both NIH and WGO-OMGE agree that a definitive diagnosis for celiac disease is confirmed when symptoms resolve with a gluten-free diet.

Management

There is agreement among all three guidelines that a lifelong gluten-free diet is the most effective treatment for celiac disease. All three also agree that in order to achieve patient adherence to the diet, the patient needs clinical follow-up, treatment of nutritional deficiencies, and appropriate patient education and support through skilled dieticians and celiac support groups.

Areas of Differences

Screening/Assessment

While NIH and AGA both recommend screening in symptomatic high risk patients, NIH does not recommend testing in patients with osteoporosis, stating that "data does not indicate a significantly increased prevalence of celiac disease in the general population of people with osteoporosis." In contrast, AGA recommends testing in patients with osteoporosis, especially with premature osteoporosis or osteomalacia, stating that "the prevalence of celiac disease may be increased in patients with osteoporosis (~1.5% to 3%)." WGO-OMGE similarly recommends that a diagnosis of CD be considered in patients with osteoporosis or osteomalacia.

Diagnostic Testing

AGA is the only group to state that the best serologic test overall (less time consuming and less operator dependent) is the IgA tTG. NIH recommends IgA EMA and IgA tTG, stating that both tests have equivalent diagnostic accuracy. WGO-OMGE also recommends both IgA EMA and IgA tTG, but states that IgA EMA testing is moderately sensitive and highly specific, while IgA tTG testing is highly sensitive and specific for the diagnosis of celiac disease. WGO-OMGE also states that the dot ELISA is the easiest and cheapest serological test, for low-income regions.

WGO-OMGE mentions the presence of HLA-DQ2 or -DQ8 molecules in patients with celiac disease but does not recommend HLA testing to exclude the presence of celiac disease as AGA and NIH do.

Management

There are no significant differences between the 3 groups in regard to the management of celiac disease.

The only difference may be in the treatment of refractory celiac disease, which is the persistence of symptoms and intestinal inflammation despite a gluten-free diet. AGA suggests that the optimal therapy is not known but frequently includes immunosuppression; whereas, NIH and WGO-OMGE do not address treatment. NIH states that refractory celiac disease may occur in the context of ulcerative jejunitis, or it may be an early manifestation of intestinal lymphoma. WGO-OMGE states that refractory celiac disease is considered to be a form of low-grade intraepithelial lymphoma.

Conclusion

All three groups recommend serologic testing using anti-tissue transglutaminase antibody tests (IgA EMA, IgA tTG), along with intestinal biopsy for diagnosis of celiac disease and a treatment plan that includes a lifelong gluten-free diet with follow-up and support to maintain patient adherence. None of the guidelines recommend general population screening for celiac disease at this time.

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