

Celiac Disease Diagnosis and Management

A 46-Year-Old Woman With Anemia

Daniel Leffler, MD, MS, Discussant

DR SHIP: Ms J is a 46-year-old woman recently diagnosed with celiac disease. She lives in the greater Boston area and has private insurance. Ms J has generally been in good health. She has been anemic since her first pregnancy 20 years ago. She was pregnant 3 times subsequently but miscarried each time, always in the second trimester. She transferred to a new physician about 5 years ago. At that time, her hematocrit percentage was in the low 30s. Her indexes were normal, and although her ferritin level was low (7.2 ng/mL), her iron level increased into the normal range with supplementation. She reported heavy menses at the time, which was thought to be the cause of her anemia.

In March 2010, Ms J presented for routine care and was found to have a hematocrit of 26% with a mean corpuscular volume of 78 fL. She reported inability to tolerate iron because of constipation. She also reported much lighter menses and intermittent epigastric discomfort, for which a trial of a proton pump inhibitor was recommended. Given these findings, her internist referred her for an endoscopy and, because of a family history of colon cancer, a colonoscopy.

Her colonoscopy results were normal and a biopsy taken during her endoscopy showed villous shortening and an increased number of intraepithelial lymphocytes, consistent with celiac disease (FIGURE 1). Further testing revealed a normal tissue transglutaminase (tTG) IgA level at 14 units (reference range, 0-19) but an elevated anti-deamidated gliadin peptide (DGP) level (IgA/IgG) at 104 units (reference range, 0-19).

Ms J was diagnosed with celiac disease and was instructed to follow a gluten-free diet. Her daughter was tested for celiac disease and had a negative result.

Ms J's medical history is notable for hypertension and mild, situational depression. Her medications include hydrochlorothiazide, 25 mg/d; lisinopril, 10 mg/d; and iron, 6 tablets/d. She has no drug allergies. She does not smoke or drink alcohol.

See also Patient Page.



CME available online at www.jamaarchivescme.com and questions on p 1606.

Celiac disease is one of the most prevalent autoimmune gastrointestinal disorders, but as the case of Ms J illustrates, diagnosis is often delayed or missed. Based on serologic studies, the prevalence of celiac disease in many populations is estimated to be approximately 1% and has been increasing steadily over the last 50 years. Evaluation for celiac disease is generally straightforward and uses commonly available serologic tests; however, the signs and symptoms of celiac disease are nonspecific and highly heterogeneous, making diagnosis difficult. Although celiac disease is often considered a mild disorder treatable with simple dietary changes, in reality celiac disease imparts considerable risks, including reduced bone mineral density, impaired quality of life, and increased overall mortality. In addition, a gluten-free diet is highly burdensome and can profoundly affect patients and their families. For these reasons, care of individuals with celiac disease requires prompt diagnosis and ongoing multidisciplinary management.

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MS J: HER VIEW

When I first was told that I had celiac disease, I didn't really know what to think because I hadn't really heard of it before. They told me that I was never going to be able to have any type of wheat, rye, and barley products again. At first I thought, it's just a temporary thing, and then, when I realized that I could never really have any of that food again for the rest of my life, I was in denial. I was like, "Oh, wow,"

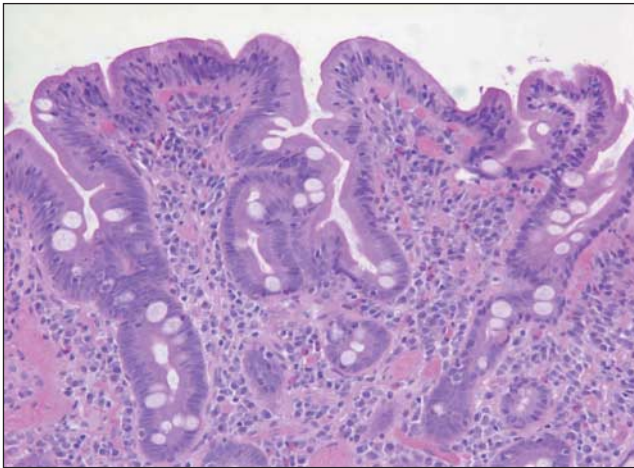
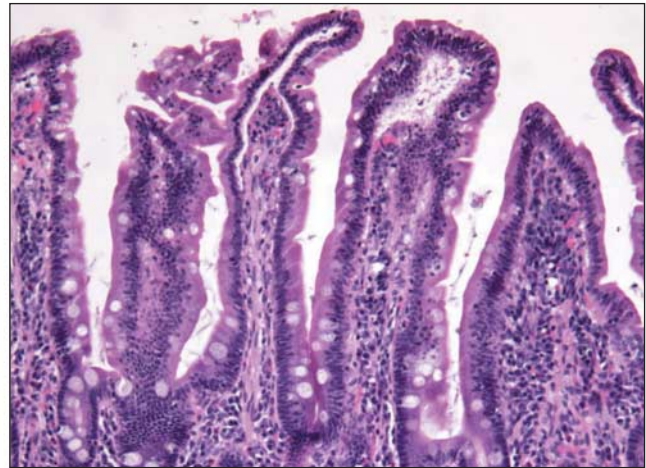
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Figure 1. Duodenal Biopsy Specimens**A** Ms J's duodenal biopsy specimen**B** Example of normal duodenal biopsy specimen

A, Duodenal biopsy specimen from Ms J's upper endoscopy showing villous shortening and an increased number of intraepithelial lymphocytes, consistent with celiac disease. B, Biopsy specimen of normal duodenum for comparison. Magnification $\times 200$; hematoxylin-eosin stain.

but I started the diet right away. Since I've been on it, I dropped 15 pounds, my iron level has gone up, and my joints don't hurt any more. I just feel overall better than I did.

It's very difficult to be on a gluten-free diet. I find it very hard to go out to eat. We used to go out to eat as a family once a week; now, it's very difficult because not all restaurants have gluten-free menus, and the ones that do have gluten-free, you don't know what goes on in the kitchen. I did cheat once when I was on vacation. After being off of the gluten for 2 or 3 months and then cheating, I felt really bad the next day. Shopping at the grocery store is also very difficult. It's very expensive, especially in this type of economy. One loaf of bread is \$7!

This really is a lifestyle change, and the hardest thing is to know that I can never eat these items for the rest of my life. Some underlying questions I have are what kind of damage has it done not being diagnosed earlier? Is it reversible? Also, I would like to know why I had the miscarriages. Is there a connection?

AT THE CROSSROADS: QUESTIONS FOR DR LEFFLER

What are the epidemiology and pathophysiology of celiac disease? Which symptoms should prompt a clinician to test for celiac disease? How is the diagnosis of celiac disease made? What are the specificity and sensitivity of tTG antibody testing? When is a small intestinal biopsy indicated? Are there any populations that should be screened for celiac disease? Should family members be tested? Once a diagnosis is made, what treatment is possible other than avoidance of gluten? Is adherence to the gluten-free diet ever optional? What are the harms of cheating? What testing should patients with

celiac disease undergo and until what age? What does the future hold? What do you recommend for Ms J?

DR LEFFLER: Throughout the article, the GRADE system¹ is used to describe the evidence that supports the statements. All statements apply to both children and adults except where specifically noted.

(A) High quality: Further research is very unlikely to change confidence in the estimate of effect.

(B) Moderate quality: Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.

(C) Low quality: Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.

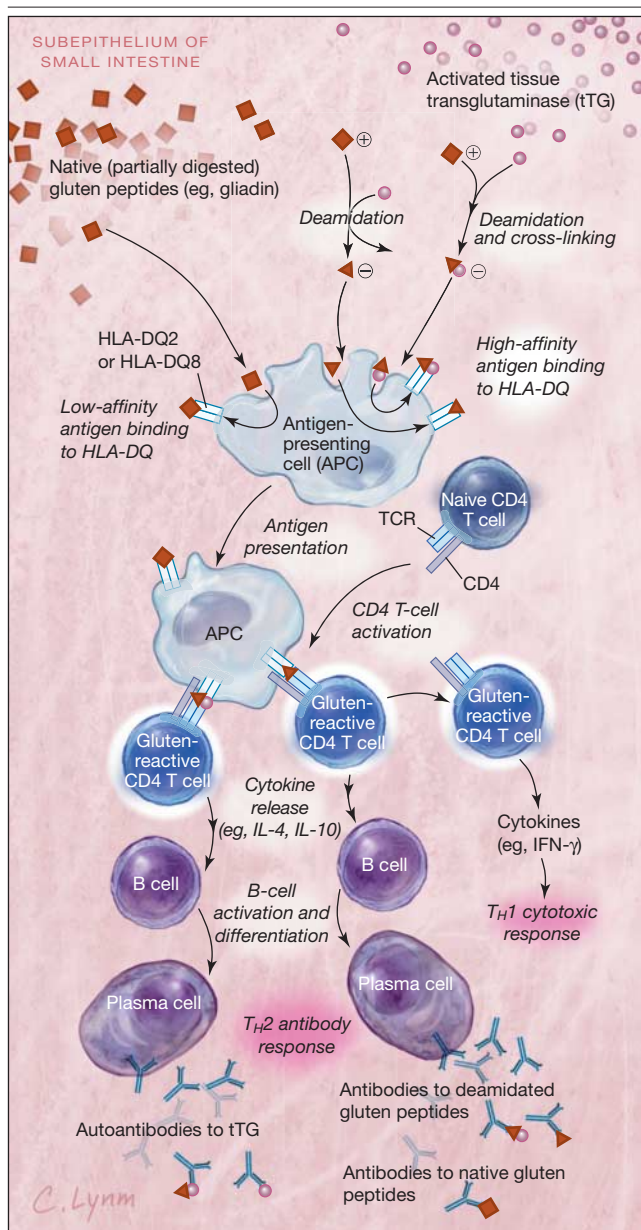
(D) Very low quality: Any estimate of effect is very uncertain.

Epidemiology and Pathophysiology

Ms J: *What kind of disease is this?*

Celiac disease has long been considered a rare disorder of childhood. Significant advances in the understanding of celiac disease have refuted this notion, and the currently accepted prevalence of celiac disease is approximately 1% to 2% of the general population in many regions of the world, including North and South America, Europe, North Africa, the Middle East, and India.^{2,3} The increased diagnosis of celiac disease is related both to improved testing and to true increases in celiac disease prevalence.⁴ Although inflammation is induced by the foreign protein gluten, celiac disease is best understood as a complex autoimmune disorder rather than an allergy because autoantibodies to tTG are central to the disease process (FIGURE 2). Gluten,

Figure 2. Antigen Presentation and Production of Antibodies to Gluten Peptides and Tissue Transglutaminase (tTG)



In the subepithelium of the small intestine, native (partially digested) gluten peptides are deamidated by the enzyme tTG. While tTG is ubiquitous, it is predominantly stored intracellularly in an inactive state and released in the presence of inflammation and activated by higher levels of extracellular calcium ions. Deamidation leads to change in shape and charge of the gluten peptides, permitting high-affinity binding to HLA-DQ2 and -DQ8 on APCs such as dendritic cells and macrophages. Only HLA-DQ2 and -DQ8 are able to bind gluten peptides strongly enough to trigger an inflammatory reaction, so the presence of at least 1 of these molecules is a prerequisite for development of celiac disease. Naive T cells that have been activated by deamidated gluten presented by APCs are then able to stimulate both a T_H1 cytotoxic and T_H2 humoral antibody response. The T_H2 response leads to production of antibodies against native gluten peptide, deamidated gluten peptide, and tTG. Antibodies to the self-protein tTG are produced because tTG is often still complexed with deamidated gluten peptides during presentation by APCs. This directed anti-self immune response is the major autoimmune component of celiac disease. TCR indicates T-cell receptor; IFN, interferon.

the major protein in wheat, rye, barley, and related grains, is poorly digested and reaches the intestinal lumen in large polypeptides. In individuals with celiac disease, gluten peptides pass through the mucosa of the small intestine into the submucosa. In the submucosa, gluten peptides are modified by the common enzyme tTG and become able to bind with high affinity to HLA antigen DQ2 and DQ8 molecules on antigen-presenting cells, stimulating both cell-mediated and humoral immune reactions.⁵

Symptoms

Ms J: *I didn't have any diarrhea or constipation; I think that's what threw my PCP off.*

Although discoveries in the pathophysiology of celiac disease have led to accurate serologic testing, the differential diagnosis of the signs and symptoms of celiac disease is broad and challenging for clinicians. Infants and children typically present with predominant symptoms of malabsorption, including diarrhea and failure to thrive; however, the list of signs and symptoms associated with celiac disease in older children and adults is vast and new associations are reported regularly (TABLE 1).

Testing for celiac disease in all patients who present with any of the dozens of possible signs and symptoms would quickly approach population screening, an approach not currently supported by available evidence, as discussed herein. Deciding when to test for celiac disease and when to refer for further evaluation is challenging, contributing to an average of 11 years of symptoms prior to diagnosis^{47,48} and, often, a complete failure to test for celiac disease.

Fortunately, types of presentation can be divided into 3 general categories based on risk of celiac disease as described in Table 1, and these can be helpful in guiding effective celiac disease testing and referral. The individuals at highest risk tend to have complicated enough cases to warrant referral to a gastroenterologist regardless of concern for celiac disease. Indeed, in the case of Ms J, the combination of difficult-to-treat iron deficiency anemia and upper gastrointestinal symptoms led to referral to a gastroenterologist, at which point a diagnosis of celiac disease was promptly made.

Diagnosis

Prior to the 1980s, a lack of noninvasive testing for celiac disease severely limited diagnosis rates. Antigliadin antibody testing became available in the mid-1980s, but the positive predictive value in moderate-risk groups is less than 30%, precluding efficient diagnosis (A).² Endomysial antibody testing became available in the early 1990s and was reported to have sensitivity and specificity of higher than 95%, but use was curtailed by cost and interpretability issues (A).²

In 1997, tTG was determined to be the major autoantigen in celiac disease⁴⁹; shortly thereafter, assays for anti-

tTG antibodies were developed. Current tTG tests are based on IgA antibodies to recombinant human tTG. In most studies, sensitivity and specificity are higher than 90% and 95%, respectively,^{2,50} which equates to a positive predictive value of approximately 75% and a negative predictive value of 99% in moderate-risk populations, given a 5% pretest probability (A).

Although tTG IgA testing is generally accepted to be the initial test of choice for celiac disease in most situations,^{51,52} the case of Ms J illustrates some important caveats. First, approximately 5% of individuals with celiac disease have negative results, and all serologic tests

appear to be less sensitive in children younger than 2 years (A).⁵³ For this reason, when the pretest probability is high, as in individuals such as Ms J with iron deficiency anemia and gastrointestinal symptoms or any of the other conditions listed in the first row of Table 1, a normal tTG IgA test result is not sufficiently specific to rule out celiac disease, so upper endoscopy with duodenal biopsy should be strongly considered (B). Conversely, while well described, tTG-negative celiac disease remains uncommon and other causes of small intestinal villous atrophy also should be considered.⁵⁴ To confirm the diagnosis of celiac disease, patients with intestinal damage

Table 1. Presenting Signs and Symptoms and Pretest Probability of Celiac Disease^a

Pretest Probability (GRADE Score) ^b	Risk Factors	Evidence Notes	Comments
High: Testing for celiac disease is always warranted (A). Negative serologic test result may not adequately rule out celiac disease (B).	Chronic gastrointestinal symptoms with a family history of celiac disease or a personal history of autoimmune disease or IgA deficiency ^{6,7} Biopsy-proven dermatitis herpetiformis ⁸ Chronic diarrhea ⁹ Failure to thrive in children ¹⁰ Iron deficiency anemia refractory to oral supplementation ¹¹	Risk of celiac disease in first- and second-degree relatives is approximately 8% and 4%, respectively, ^{12,13} and increases to 20% in symptomatic family members. ¹⁴ Testing for celiac disease in patients with classic symptoms is thought to be cost-effective. ¹⁵	Risk in these populations is generally 10% or higher.
Medium: Testing for celiac disease is generally warranted (B). Negative serologic test result adequately rules out celiac disease (A).	Irritable bowel syndrome ^{16,17} Elevated liver function test results ¹⁸ Iron deficiency anemia ¹⁹ Fatigue/lethargy ²⁰ Chronic gastrointestinal symptoms without a family history of celiac disease or a personal history of autoimmune disease ^{13,21} Peripheral neuropathy ²² Ataxia ²³ Dental enamel defects ²⁴ Recurrent aphthous ulcerations ²⁴ Hyposplenism ^{25,26} Fertility abnormalities ²⁷ Down or Turner syndrome ²⁸ Known IgA deficiency ⁷ Microscopic colitis ²⁹	Two separate studies of cost-effectiveness of celiac testing in irritable bowel syndrome concluded that testing is generally warranted in this population. ^{17,30}	Risk in these populations is generally 4%-10%. Guidelines published by the American College of Gastroenterology in 2009 recommend celiac disease testing for all patients with diarrhea and presumed irritable bowel syndrome. ³¹
Low: Testing for celiac disease is warranted only after excluding more likely etiologies or with coexistent risk factors (B). Negative serologic test result adequately rules out celiac disease (A).	Osteopenia/osteoporosis ³² Fibromyalgia ³³ Chronic fatigue syndrome ³⁴ Heartburn/gastroesophageal reflux disease ³⁵ Acute or chronic pancreatitis ³⁶ Alopecia ³⁷ Myalgias/artralgias Autoimmune liver disease ¹⁸ Personal history of autoimmune disease or connective tissue disease without ongoing unexplained symptoms ^{38,39} Skin lesions other than dermatitis herpetiformis ⁴⁰ Headaches including migraines ⁴¹ Mood disorders ^{39,42} Attention-deficit/hyperactivity disorder/cognitive impairment ^{43,44} Epilepsy ⁴⁵ Restless legs syndrome ⁴⁶		Risk in these populations is generally <4%. Few cost-effectiveness analyses in celiac disease testing have been performed but limited data suggest that routine serologic testing becomes cost-effective at a prevalence of >4%.

^aCeliac disease is rare in individuals of pure East Asian, Southeast Asian, sub-Saharan African, and Inuit descent.³ Recommendations do not apply to these groups.

^bThe GRADE scoring system is as follows: (A) High quality: Further research is very unlikely to change confidence in the estimate of effect. (B) Moderate quality: Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate. (C) Low quality: Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. (D) Very low quality: Any estimate of effect is very uncertain.

suggestive of celiac disease but who have negative tTG IgA results should have further evaluation, including total IgA measurement, tests for antibodies to DGP, tests for celiac disease–related HLA DQ2 and HLA DQ8 (the absence of which excludes celiac disease), and assessment of clinical and histologic improvement with a gluten-free diet (B).²

Finally, symptomatic response to a gluten-free diet is neither a sensitive nor a specific test for celiac disease for a number of reasons. First, conditions including food allergy and, much more commonly, non-celiac gluten sensitivity improve with a gluten-free diet.⁵⁵⁻⁵⁷ However, at least 10% of patients with celiac disease do not fully respond to dietary modification alone because of either inadvertent gluten exposure or coexisting conditions, including irritable bowel syndrome.⁵⁸ Second, patients and clinicians should be aware that both serologic and histologic measures normalize with a gluten-free diet, so testing for celiac disease should be completed prior to dietary modification (A).

Given the accuracy of serologic testing, a common question is why small intestinal biopsy remains recommended for celiac disease diagnosis. Although some suggest that biopsy should no longer be required,⁵⁹ it remains the gold standard for diagnosis for a number of reasons.^{51,52,60} Although the sensitivity of tTG IgA testing is high, in most risk groups the positive predictive value of a positive test result is only about 75%, and spurious positive tTG titers can be seen in cirrhosis⁶¹ and congestive heart failure⁶² and after enteric infections.⁶³ Additionally, although celiac disease may be misconstrued as “benign,” with little harm in false-positive diagnosis, in reality misdiagnosis of celiac disease is deleterious on multiple levels. First, as discussed herein, the burden of a gluten-free diet is substantial. Second, celiac disease is associated with adverse outcomes including refractory celiac disease⁶⁴ and malignancies,⁶⁵ so while overall outcomes in celiac disease are generally good,^{65,66} mortality rates may be persistently elevated⁶⁷ and concern regarding complications can lead to extensive medical testing. Patients with confirmed celiac disease commonly experience episodes of recurrent symptoms, and intestinal histologic evaluation at diagnosis is often vital in determination of potential causes.⁵⁸ False-positive diagnosis can also lead directly to increased health care costs because individuals with celiac disease are routinely recommended to have tests such as vitamin level and bone mineral density (BMD) evaluations, which may not be otherwise necessary.⁵² Finally, because celiac disease is hereditary, with an approximate 8% risk in first-degree family members and 4% risk in second-degree family members,¹² a single false-positive diagnosis can precipitate a string of unnecessary tests in patients’ relatives. For all of these reasons, the diagnosis of celiac disease requires duodenal biopsy consistent with celiac disease and either a positive serologic test result or response to a gluten-free diet (B).⁵²

Screening Populations or Family Members

Ms J: *No one else in my family has been tested except for my daughter.*

Screening for celiac disease is controversial.^{68,69} The World Health Organization criteria for screening of non-communicable diseases can be summarized by the following requirements⁷⁰: (1) The disease must be common and well defined. (2) Screening tests must be safe, simple, and highly accurate. (3) Both disease testing and treatment must be culturally acceptable and equitable. (4) Treatment for the disease must be available. (5) Early clinical detection must be difficult. (6) If not recognized, the disease could result in severe complications difficult to manage. (7) The overall program for testing and treatment should be cost-effective.

It is tempting to conclude that there are sufficient data to support population screening for celiac disease. First, celiac disease clearly is difficult to detect based on the heterogeneity of presentation as described herein. Second, celiac disease is common and causes significant morbidity. Third, modern serologic tests for celiac disease are among the most accurate available for any autoimmune or inflammatory disorder. Fourth, treatment with a gluten-free diet is effective in the majority of patients. Fifth, if the disease is not recognized, complications including osteoporosis, growth impairment, fertility issues, and malignancy can occur. Sixth, tTG IgA testing is relatively inexpensive, costing approximately the same as a lipid panel in most areas, and Markov models suggest that given the mortality associated with untreated symptomatic celiac disease, screening would be cost-effective.¹⁵

Currently, however, available data regarding the morbidity of undiagnosed and untreated celiac disease are based almost entirely on patients with clinically diagnosed symptomatic celiac disease. A large proportion of individuals detected in a mass screening effort would be expected to be minimally symptomatic or asymptomatic, and data suggest that this group may not have the same risks as those with clinically evident celiac disease.^{71,72} The few prospective studies that have evaluated screening for celiac disease in adults have not conclusively found screening to be beneficial.^{73,74} A final complexity is that celiac disease can present at any age, so the timing and testing intervals would need to be determined to balance delayed diagnosis vs cost. For these reasons, the currently accepted strategy for celiac diagnosis is aggressive case finding in individuals presenting with signs and symptoms suggestive of celiac disease (C).^{52,60} Fortunately, although diagnosis is often markedly delayed,^{47,48} studies suggest that with proper clinician education, case finding can be highly effective.^{6,75}

Testing of all close relatives of patients with celiac disease should be considered separately from population screening because of the increased risk of celiac disease in first- and second-degree relatives.⁵² In children and adolescents, because of the risk of permanent impairment of

growth and development, guidelines recommend testing for celiac disease every 2 to 3 years or at onset of new symptoms in children with a family history of celiac disease or comorbid conditions (B).^{28,60} In adults, testing is reserved for those with signs or symptoms suggestive of celiac disease (C),⁵² although with the increasing number of celiac associations, clinicians should maintain a very low threshold for testing.

There are 2 celiac testing strategies for individuals at risk because of family history. The most common strategy is serologic testing identical to that for any symptomatic patient (B). However, serologic testing and intestinal biopsy are both diet-dependent and rule out only currently active celiac disease. A second strategy is to test for the presence of HLA DQ2 and HLA DQ8, either of which is prerequisite for the development of celiac disease.⁵² Nearly 40% of the general population has HLA DQ2 or HLA DQ8; therefore, a negative test result essentially rules out celiac disease but a positive test result is not useful in guiding future care (B).⁵²

Treatment Options

Ms J: *It's very difficult to be on a gluten-free diet . . . it's very difficult to go out to eat. Shopping . . . now takes an hour and a half rather than 20 minutes and is very expensive and confusing . . . you have to really read the labels and be vigilant . . . I did cheat once and I felt really bad.*

Currently, the only accepted therapy for celiac disease is strict adherence to a gluten-free diet.⁵² Although the ability to treat a disease without medications is attractive, as Ms J reports, adherence to a gluten-free diet is quite difficult. The cost of the gluten-free diet is 2 to 3 times that of a standard diet,⁷⁶ and while a gluten-free diet is subsidized in many European countries, elsewhere expense represents a significant hardship. Additionally, although a balanced gluten-free diet can be quite healthy, in many individuals the loss of common whole grains and inconsistent fortification result in failure to meet the recommended daily intakes of many nutrients (B).^{77,78} This risk can be mitigated with proper counseling and motivation, and cost can be minimized and nutritional value maximized with use of raw ingredients. Regardless, the need to avoid specific foods is a profound social stress for children and adults that continues to be troubling years after adoption of a gluten-free diet (A).⁷⁹⁻⁸¹

Even for those making substantial effort to maintain a strict gluten-free diet, the degree of adherence necessary is challenging. It has been shown that as little as the amount of gluten found in one-thirtieth of a slice of bread is enough to cause intestinal damage (B),^{82,83} and to make matters worse, gluten is a ubiquitous ingredient/contaminant in many foods and even medications.^{84,85} For these reasons, an absolute gluten-free diet is probably not attainable, and the addition of purposeful gluten consumption or "cheating" on top of unavoidable exposure should not be endorsed. A strict gluten-free diet should be strongly encouraged

because nonadherence is common at all ages^{81,86} and is associated with a lax attitude toward gluten exposure,⁸⁷ and even inadvertent gluten exposure commonly results in recurrent symptoms.^{58,88}

For clinically evident celiac disease, evidence exists for the beneficial effect of a gluten-free diet on symptoms⁸⁹ and quality of life,^{73,74} and the overall standardized mortality rate has been shown to decrease from more than 2.8 (95% CI, 2.51-3.11) to 1.22 (95% CI, 1.13-1.32) after 1 year of treatment (A).^{65,67} However, as discussed in the section on screening, limited data suggest that asymptomatic patients may safely continue a regular diet with proper monitoring,⁷² and for patients in whom celiac disease is diagnosed based on screening antibodies alone and who have no evident symptoms or nutritional abnormalities, discussion of the risks and benefits of monitoring with a regular diet rather than immediate adoption of the gluten-free diet is reasonable (C).

Ongoing Monitoring

Ms J: *What am I supposed to do now?*

While there is general consensus on establishing the diagnosis of celiac disease and dietary treatment, data on optimal monitoring strategies are limited and subsequently guidelines vary (TABLE 2). With the development of the gluten-free diet in the 1940s, celiac disease changed from a highly morbid childhood disease with a reported case-fatality rate of 9%⁹⁴ to one with a very modestly increased standardized mortality rate of 1.39 (95% CI, 1.33-1.45).⁶⁷ This treatment success suggested that there was little to be gained by further research on treatment, and over the following decades most efforts focused on epidemiology, pathophysiology, and diagnosis. In recent years, studies of patients followed up into adulthood or with diagnoses made during adulthood have suggested the need for closer monitoring,^{67,95} and several consensus guidelines have been developed (Table 2). Overall, given the limitations of available data, ongoing care of patients with celiac disease should be individualized. All available guidelines suggest regular celiac disease evaluation by a dietitian (C) and most by a physician, as well as tTG tests (B) and nutrient level tests (C). Repeat intestinal biopsy is not recommended by most guidelines in adult or pediatric patients who respond clinically and serologically to treatment (B).

What Does the Future Hold?

Ms J: *What are they going to do—are they going to give you a pill?*

Knowing both the instigating antigen (gluten) and the end result of immune dysregulation (enteropathy and autoantibody production), the pathophysiology of celiac disease is substantially better understood than for other autoimmune/inflammatory disorders.⁹⁶ Advances in diagnosis have propelled celiac disease from an uncommon disorder to one of the most common and most rapidly increas-

ing gastroenterological disorders. Although the gluten-free diet is safe, it is clearly not an optimal treatment, imparting significant burden to patients and failing to achieve either complete symptom resolution or intestinal healing in up to 30% of patients (B).^{58,95} The combination of comprehensive understanding of celiac disease and a need for adjunctive or alternative treatments to a gluten-free diet has spurred much recent work in the area of celiac therapeutics. Therapies currently in testing include enzymes to degrade gluten in the stomach prior to immune presentation in the small intestine, molecules to enhance the tight junctions between enterocytes barring gluten entry, methods of detoxifying gluten in wheat or during food processing, and reinduction of immune tolerance through “vaccination” with gluten peptides, among other possibilities (FIGURE 3).⁹⁷ Which of these first-generation therapies will hold substantial benefit for the millions with celiac disease is unknown, but the thorough understanding of the pathophysiology of celiac disease will hopefully lead to a durable cure and help pave the way for improved treatments of many other autoimmune/inflammatory disorders.

RECOMMENDATIONS FOR MS J

Ms J: *It would have been helpful if I had had a chance to speak with a dietitian.*

Based on symptoms, positive serologic test results for celiac disease, and intestinal histologic findings, Ms J meets criteria for celiac disease. She should be informed that she has a lifelong autoimmune disorder that necessitates strict avoidance of all foods containing any amount of wheat, rye, or barley (A). Ms J should also be referred to a dietitian skilled in celiac disease counseling and to a regional celiac advocacy group (B) (for patient resources, see the eAppendix at <http://www.jama.com>). It is likely that Ms J has had celiac disease for many years, and untreated celiac disease may have contributed to her recurrent miscarriages (C).^{98,99} Fortunately, with adherence to a gluten-free diet, proper support, and nutritional supplementation, she can expect to achieve clinical remission. Although no empirical evidence exists, based on expert opinion I also recommend monitoring of vitamin levels including 25-hydroxyvitamin D, iron, and other nutrients based on symptoms (C).^{52,91} Because of the high prevalence of nutritional deficiencies, I

Table 2. Guideline-Recommended Monitoring of Individuals With Celiac Disease^a

Strength of Recommendation	Recommendation (GRADE Score) ^b	Comments
Recommended (suggested by 5-6 of the 6 available guidelines)	Lifelong adherence to a gluten-free diet (A) ^{c,d,e,f,g,h} Regular visit to dietitian knowledgeable in celiac disease (C) ^{c,d,e,f,g,h} Monitoring of gastrointestinal symptoms (C) ^{c,d,e,f,g} Annual monitoring of gluten-free diet adherence (C) ^{c,d,e,f,g} Monitoring of tTG (B) ^{c,d,e,f,g} Regular laboratory testing of nutritional status (C) ^{c,e,f,g,h} Bone density evaluation within 1 y of treatment (in adults only) (B) ^{c,e,f,g,h}	Although most guidelines suggest laboratory testing of nutritional status, specific recommendations vary greatly. Ferritin, vitamin B ₁₂ , folate, and 25-hydroxyvitamin D are considered routine. Other tests to consider include zinc, calcium, copper, thiamin, albumin, and vitamins B ₆ , A, E, and K.
Consider (suggested by 2-4 of the 6 available guidelines)	Regular visit with physician for celiac disease ^{c,d,e,g} (C) Monitoring of anthropometrics ^{d,e,f,g} (C) Referral to celiac disease advocacy group (C) ^{c,d,e,h} Monitoring of celiac disease–related quality of life (C) ^{e,f} Monitoring of liver function (C) ^{e,g} Monitoring of hemoglobin (C) ^{e,g} Monitoring of lipid levels (in adults only) (C) ^{e,f}	Routine celiac disease monitoring by a physician can be considered optional if the patient consults an expert celiac disease dietitian. Timing of follow-up by a dietitian or physician is variable, but a common schedule is at diagnosis, 3-6 mo postdiagnosis for the first year or until in clinical remission, and annually thereafter.
Not widely recommended (suggested by 1 of the 6 available guidelines)	Daily multivitamin and mineral supplement (C) ^f Assessment for related autoimmune and endocrine disorders (D) ^f Influenza and pneumonia vaccination (C) ^g Initial testing of prothrombin time (D) ^e Regular monitoring of electrolytes and renal function (D) ^f Repeat intestinal biopsy (D) ^g	Most publications do not focus on nutritional therapy and, although suggested in only the American Dietetic Association guideline, recommendation of a multivitamin and calcium/vitamin D is common. Vaccination is recommended because of association of celiac disease with increased risk of infection and impaired spleen function.

Abbreviation: tTg, tissue transglutaminase.

^aGuidelines referenced are the most recently published. All guidelines apply to both adults and children unless otherwise specified.

^bThe GRADE scoring system is as follows: (A) High quality: Further research is very unlikely to change confidence in the estimate of effect. (B) Moderate quality: Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate. (C) Low quality: Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. (D) Very low quality: Any estimate of effect is very uncertain.

^cRecommended in Rostom et al.⁵²

^dRecommended in Hill et al.²⁸

^eRecommended by the National Institutes of Health Consensus Development Conference on Celiac Disease.⁹⁰

^fRecommended by the American Dietetic Association.⁹¹

^gRecommended by the Primary Care Society for Gastroenterology.⁹²

^hRecommended by the World Gastroenterology Organisation.⁹³

also suggest routine supplementation with a multivitamin and additional vitamin D and calcium with a goal 25-hydroxyvitamin D level of 20 to 40 ng/mL depending on known bone density and coexisting risk factors for osteopenia, as well as aggressive repletion of any other vitamins or minerals in which she is found to be deficient (C). Aside from nutritional status, thyrotropin and liver function tests should be checked at diagnosis to assess for related autoimmunity (C).^{90,91}

Her daughter is older than 18 years, so routine celiac serologic or HLA testing is unnecessary, but I would encourage her to inform her relatives that celiac disease is now in the family and that they should discuss serologic testing with their primary care physicians based on any symptoms they may be experiencing. Ms J's iron deficiency may indeed be multifactorial from both menses and celiac disease and should be monitored closely over the next few months. However, should she continue to have symptomatic anemia without rapid improvement, parenteral iron repletion should be considered. I recommend she visit her dietitian and physician approximately 6 and 12 months after diagnosis to monitor symptoms and recheck tTG IgA levels (B). I also recommend evaluation of BMD approximately 1 year after adoption of a gluten-free diet. Afterward, visits for celiac disease can be continued on an annual basis with both a dietitian and a physician knowledgeable about celiac disease.

QUESTIONS AND DISCUSSION

Ms J: Could my miscarriages have been related to celiac disease?

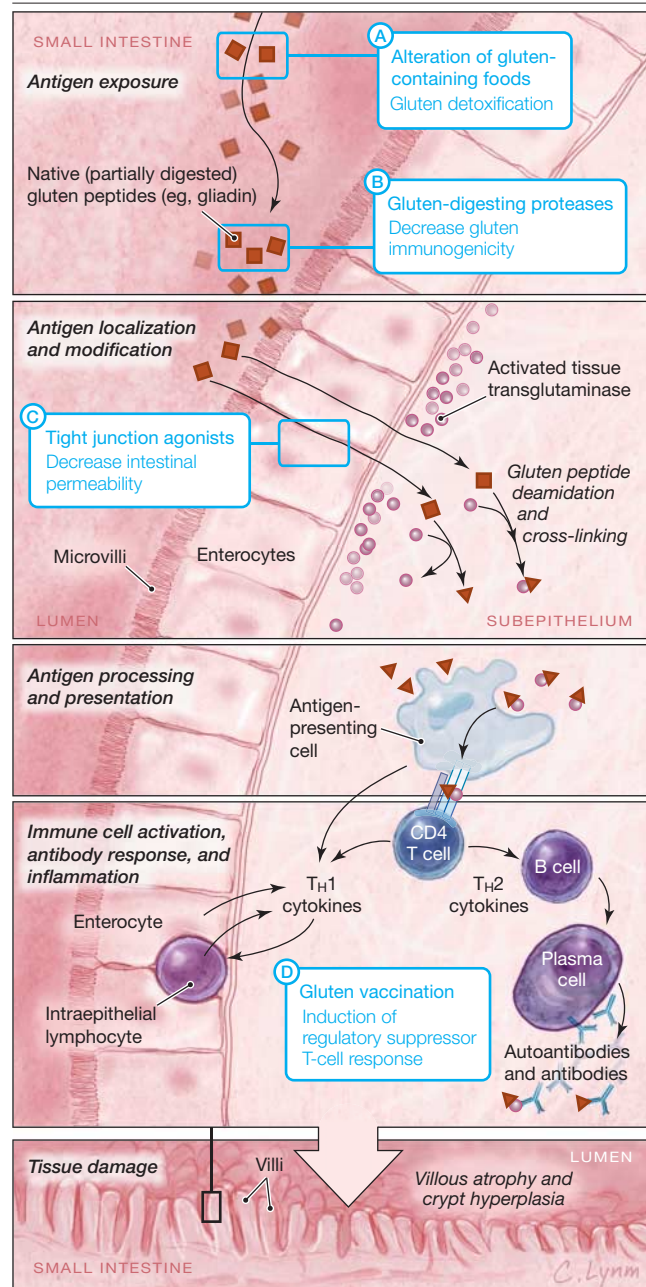
DR LEFFLER: Currently, the typical new diagnosis of celiac disease is in a woman about 40 years old who has had symptoms of celiac disease for more than a decade. Given that active celiac disease has nutritional and direct inflammatory consequences on fertility,^{27,100} the reproductive life of many patients is irreversibly affected (B). In particular, the risk of miscarriage appears higher in women with untreated celiac disease compared with the general population (C).¹⁰¹ For these reasons, clinicians should maintain a very low threshold for celiac disease testing in this population.

Ms J: Has my body sustained any irreversible damage from celiac disease over the years?

DR LEFFLER: The small intestinal mucosa has enormous regenerative capacity in both health and disease. Even individuals with long-standing, severe celiac enteropathy can expect to achieve complete or near complete intestinal healing with gluten avoidance and nutritional support, although the length of time to healing varies from less than 1 year to more than 5 years and healing is associated with younger age at diagnosis and improved gluten-free diet adherence (B).^{95,102}

Outside of the intestine, however, healing is not always ensured. A number of extraintestinal manifestations of ce-

Figure 3. Pathophysiology of Celiac Disease and Potential Nondietary Therapies Being Tested in Phase 1 or 2 Clinical Trials



Gluten peptides are poorly digested by mammalian digestive enzymes and reach the small intestinal mucosa as large polypeptides. Gluten peptides are able to cross the mucosa into the subepithelium by transcellular and/or paracellular pathways. In the subepithelium, gluten peptides are deamidated by tissue transglutaminase (Figure 2) and trigger cytotoxicity leading to mucosal damage and humoral immunity leading to antibody production. Detailed understanding of the pathophysiology of celiac disease has allowed for creation of highly targeted potential nondietary therapies (blue boxes). These include (A) alteration of gluten-containing foods through the use of alternative or genetically modified wheat varieties or through specialized food processing techniques; (B) degradation of gluten proteins in the stomach and small intestinal lumen by selected proteases; (C) preventing gluten passage into the subepithelium of the small intestine through the use of tight junction agonists; and (D) reinduction of tolerance to gluten through immune desensitization.

liac disease, such as dermatitis herpetiformis, anemia, and joint pain, typically improve significantly or resolve within the first year of treatment, as was seen in Ms J (B).¹⁰³ One of the most common associations with celiac disease is reduced BMD, which is seen in more than half of patients at diagnosis.¹⁰⁴ Although BMD often improves significantly during the first year of treatment with a gluten-free diet, up to 21% of patients have persistent osteoporosis (B).¹⁰⁴ There are multiple neurologic manifestations of celiac disease, including peripheral neuropathy and headaches, that eventually resolve, while case studies suggest that other manifestations including ataxia may stabilize but rarely improve (B).¹⁰⁵ Finally, there is a potential increased risk of secondary autoimmune disorders that are related to long-standing untreated celiac disease and that, once triggered, will not respond to gluten withdrawal (D).¹⁰⁶

QUESTION: I have the sense that everyone who has anything going on is claiming to be gluten sensitive and is trying a gluten-free diet. This seems to be an epidemic that is potentially hurting a lot of people rather than helping them.

DR LEFFLER: Americans love fad diets, and there is certainly a component of that with the increased popularity of the gluten-free diet. In some ways it has been beneficial because it has greatly increased food availability for people with celiac disease. Although there is certainly a placebo component to adopting a gluten-free diet, non-celiac gluten sensitivity does appear to be a real phenomenon and studies have shown an HLA predisposition for response to gluten withdrawal.⁵⁶ A recent double-blind randomized controlled trial demonstrated that gluten can exacerbate gastrointestinal symptoms in people without celiac disease who are following a gluten-free diet (C).⁵⁵ No matter why people choose to follow a gluten-free diet, given nutritional concerns including lack of fiber and B vitamins,⁷⁷ they should be seeing a dietitian to help maintain a nutritionally sound diet (B).

QUESTION: Given that celiac disease is hard to treat, is serologic testing of any use in patients who are not doing as well as one would like? Conversely, does resolution of symptoms always reflect intestinal healing?

DR LEFFLER: Although current serologic tests are excellent at detecting untreated celiac disease, there is clear evidence that they are not accurate indicators of disease activity or adherence to the gluten-free diet (A).¹⁰⁷ Skilled dietitian evaluation remains the gold standard for this gluten-free diet assessment, although a short standardized survey is freely available and, with a predicted accuracy of 88%, is significantly more accurate than the 65% reported for tTG IgA testing (B).⁸⁷ However, lacking more sensitive noninvasive tests of intestinal health, it is still recommended to repeat tTG IgA measurements on a yearly basis,⁵² and a decrease in serologic titer during the first year of treatment is associated with gluten avoidance (B).¹⁰⁸ A persistently positive test result should prompt evaluation for a number of potential issues, the most common being gluten exposure.⁵⁸

Conversely, like many inflammatory disorders, celiac disease activity can fluctuate over time and intestinal inflammation may persist, even in individuals with normalized tTG IgA levels and resolution of symptoms.^{2,95}

QUESTION: How do we follow patients with celiac disease who are asymptomatic for the development of severe complications, specifically lymphoma?

DR LEFFLER: This is a very common concern among patients. For routine patients without refractory celiac disease, whether having had a diagnosis with symptoms and doing well by following a gluten-free diet or asymptomatic with monitoring on a normal diet, the risk of developing lymphoma is actually very low, with a rate of approximately 8 cases per 10 000 patient-years.⁶⁵ There is no indication for routine small bowel imaging or other tests for malignancy. The main complication of celiac disease, refractory celiac disease, is symptomatic by definition,⁶⁴ so for patients who are feeling well, beyond regular nutritional and celiac blood testing and a consideration of BMD evaluation, no further testing is needed (B).

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Online-Only Material: The eAppendix is available at <http://www.jama.com>.

Additional Contributions: We thank the patient for sharing her story and for providing permission to publish it.

REFERENCES

- Guyatt GH, Oxman AD, Vist GE, et al; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926.
- Leffler DA, Schuppan D. Update on serologic testing in celiac disease. *Am J Gastroenterol*. 2010;105(12):2520-2524.
- Accomando S, Cataldo F. The global village of celiac disease. *Dig Liver Dis*. 2004;36(7):492-498.
- Rubio-Tapia A, Kyle RA, Kaplan EL, et al. Increased prevalence and mortality in undiagnosed celiac disease. *Gastroenterology*. 2009;137(1):88-93.
- Sollid LM. Coeliac disease: dissecting a complex inflammatory disorder. *Nat Rev Immunol*. 2002;2(9):647-655.
- Catassi C, Kryszak D, Louis-Jacques O, et al. Detection of celiac disease in primary care: a multicenter case-finding study in North America. *Am J Gastroenterol*. 2007;102(7):1454-1460.
- Cataldo F, Marino V, Ventura A, Bottaro G, Corazza GR; Italian Society of Paediatric Gastroenterology and Hepatology and "Club del Tenue" Working Groups on Coeliac Disease. Prevalence and clinical features of selective immunoglobulin A deficiency in coeliac disease: an Italian multicentre study. *Gut*. 1998;42(3):362-365.
- Zone JJ. Skin manifestations of celiac disease. *Gastroenterology*. 2005;128(4)(suppl 1):S87-S91.
- Sabel'nikova EA, Parfenov AI, Krums LM, et al. Prevalence of celiac disease in patients with chronic diarrhea [in Russian]. *Eksp Klin Gastroenterol*. 2004;(3):31-34, 102-103.
- Catassi C, Fasano A. Celiac disease as a cause of growth retardation in childhood. *Curr Opin Pediatr*. 2004;16(4):445-449.
- Howard MR, Turnbull AJ, Morley P, Hollier P, Webb R, Clarke A. A prospective study of the prevalence of undiagnosed coeliac disease in laboratory defined iron and folate deficiency. *J Clin Pathol*. 2002;55(10):754-757.
- Dubé C, Rostom A, Sy R, et al. The prevalence of celiac disease in average-risk and at-risk Western European populations: a systematic review. *Gastroenterology*. 2005;128(4)(suppl 1):S57-S67.
- 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):286-292.
- Rostami K, Mulder CJ, van Overbeek FM, et al. Should relatives of coeliacs with mild clinical complaints undergo a small-bowel biopsy despite negative serology? *Eur J Gastroenterol Hepatol*. 2000;12(1):51-55.

15. Shamir R, Hernell O, Leshno M. Cost-effectiveness analysis of screening for celiac disease in the adult population. *Med Decis Making*. 2006;26(3):282-293.
16. Ford AC, Chey WD, Talley NJ, Malhotra A, Spiegel BM, Moayyedi P. Yield of diagnostic tests for celiac disease in individuals with symptoms suggestive of irritable bowel syndrome: systematic review and meta-analysis. *Arch Intern Med*. 2009;169(7):651-658.
17. Spiegel BM, DeRosa VP, Gralnek IM, Wang V, Dulai GS. Testing for celiac sprue in irritable bowel syndrome with predominant diarrhea: a cost-effectiveness analysis. *Gastroenterology*. 2004;126(7):1721-1732.
18. Rubio-Tapia A, Murray JA. The liver in celiac disease. *Hepatology*. 2007;46(5):1650-1658.
19. Ransford RA, Hayes M, Palmer M, Hall MJ. A controlled, prospective screening study of celiac disease presenting as iron deficiency anemia. *J Clin Gastroenterol*. 2002;35(3):228-233.
20. Sanders DS, Evans KE, Hadjivassiliou M. Fatigue in primary care: test for coeliac disease first? *BMJ*. 2010;341:c5161.
21. van der Windt DA, Jellema P, Mulder CJ, Kneepkens CM, van der Horst HE. Diagnostic testing for celiac disease among patients with abdominal symptoms: a systematic review. *JAMA*. 2010;303(17):1738-1746.
22. Hadjivassiliou M, Grünewald RA, Kandler RH, et al. Neuropathy associated with gluten sensitivity. *J Neurol Neurosurg Psychiatry*. 2006;77(11):1262-1266.
23. Hadjivassiliou M, Grünewald R, Sharrack B, et al. Gluten ataxia in perspective: epidemiology, genetic susceptibility and clinical characteristics. *Brain*. 2003;126(pt 3):685-691.
24. Cheng J, Malahias T, Brar P, Minaya MT, Green PH. The association between celiac disease, dental enamel defects, and aphthous ulcers in a United States cohort. *J Clin Gastroenterol*. 2010;44(3):191-194.
25. Ludvigsson JF, Olén O, Bell M, Ekbohm A, Montgomery SM. Coeliac disease and risk of sepsis. *Gut*. 2008;57(8):1074-1080.
26. Corazza GR, Zoli G, Di Sabatino A, Ciccocioppo R, Gasbarrini G. A reassessment of splenic hypofunction in celiac disease. *Am J Gastroenterol*. 1999;94(2):391-397.
27. Shah S, Leffler D. Celiac disease: an underappreciated issue in women's health. *Womens Health (Lond Engl)*. 2010;6(5):753-766.
28. Hill ID, Dirks MH, Liptak GS, et al; North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. Guideline for the diagnosis and treatment of celiac disease in children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr*. 2005;40(1):1-19.
29. Green PH, Yang J, Cheng J, Lee AR, Harper JW, Bhagat G. An association between microscopic colitis and celiac disease. *Clin Gastroenterol Hepatol*. 2009;7(11):1210-1216.
30. Mein SM, Ladabaum U. Serological testing for coeliac disease in patients with symptoms of irritable bowel syndrome: a cost-effectiveness analysis. *Aliment Pharmacol Ther*. 2004;19(11):1199-1210.
31. Brandt LJ, Chey WD, Foxx-Orenstein AE, et al; American College of Gastroenterology Task Force on Irritable Bowel Syndrome. An evidence-based position statement on the management of irritable bowel syndrome. *Am J Gastroenterol*. 2009;104(suppl 1):S1-S35.
32. Sanders DS, Patel D, Khan FB, et al. Case-finding for adult celiac disease in patients with reduced bone mineral density. *Dig Dis Sci*. 2005;50(3):587-592.
33. Zipser RD, Patel S, Yahya KZ, Baisch DW, Monarch E. Presentations of adult celiac disease in a nationwide patient support group. *Dig Dis Sci*. 2003;48(4):761-764.
34. Siniscalchi M, Iovino P, Tortora R, et al. Fatigue in adult coeliac disease. *Aliment Pharmacol Ther*. 2005;22(5):489-494.
35. Nachman F, Vázquez H, González A, et al. Gastroesophageal reflux symptoms in patients with celiac disease and the effects of a gluten-free diet. *Clin Gastroenterol Hepatol*. 2011;9(3):214-219.
36. Ludvigsson JF, Montgomery SM, Ekbohm A. Risk of pancreatitis in 14 000 individuals with celiac disease. *Clin Gastroenterol Hepatol*. 2007;5(11):1347-1353.
37. Collin P, Reunala T. Recognition and management of the cutaneous manifestations of celiac disease: a guide for dermatologists. *Am J Clin Dermatol*. 2003;4(1):13-20.
38. Neuhausen SL, Steele L, Ryan S, et al. Co-occurrence of celiac disease and other autoimmune diseases in celiacs and their first-degree relatives. *J Autoimmun*. 2008;31(2):160-165.
39. Garud S, Leffler D, Dennis M, et al. Interaction between psychiatric and autoimmune disorders in coeliac disease patients in the northeastern United States. *Aliment Pharmacol Ther*. 2009;29(8):898-905.
40. Abenavoli L, Proietti I, Zaccone V, Gasbarrini G, Addolorato G. Celiac disease: from gluten to skin. *Expert Rev Clin Immunol*. 2009;5(6):789-800.
41. Lionetti E, Francavilla R, Pavone P, et al. The neurology of celiac disease in childhood: what is the evidence? a systematic review and meta-analysis. *Dev Med Child Neurol*. 2010;52(8):700-707.
42. Ludvigsson JF, Reutfors J, Osby U, Ekbohm A, Montgomery SM. Coeliac disease and risk of mood disorders—a general population-based cohort study. *J Affect Disord*. 2007;99(1-3):117-126.
43. Hu WT, Murray JA, Greenaway MC, Parisi JE, Josephs KA. Cognitive impairment and celiac disease. *Arch Neurol*. 2006;63(10):1440-1446.
44. Zelnik N, Pacht A, Obeid R, Lerner A. Range of neurologic disorders in patients with celiac disease. *Pediatrics*. 2004;113(6):1672-1676.
45. Giordano L, Valotti M, Bosetti A, Accorsi P, Caimi L, Imberti L. Celiac disease-related antibodies in Italian children with epilepsy. *Pediatr Neurol*. 2009;41(1):34-36.
46. Moccia M, Pellicchia MT, Erro R, et al. Restless legs syndrome is a common feature of adult celiac disease. *Mov Disord*. 2010;25(7):877-881.
47. Cranney A, Zarkadas M, Graham ID, et al. The Canadian Celiac Health Survey. *Dig Dis Sci*. 2007;52(4):1087-1095.
48. Green PHR, Stavropoulos SN, Panagi SG, Goldstein SL, McMahon DJ, Absan H, Neugut AI. Characteristics of adult celiac disease in the USA: results of a national survey. *Am J Gastroenterol*. 2001;96(1):126-131.
49. Dieterich W, Ehnis T, Bauer M, et al. Identification of tissue transglutaminase as the autoantigen of celiac disease. *Nat Med*. 1997;3(7):797-801.
50. Volta U, Fabbri A, Parisi C, et al. Old and new serological tests for celiac disease screening. *Expert Rev Gastroenterol Hepatol*. 2010;4(1):31-35.
51. National Institute for Health and Clinical Excellence. Coeliac disease: recognition and assessment of coeliac disease. <http://guidance.nice.org.uk/CG86/Guidance/pdf/English>. Accessed August 22, 2011.
52. Rostom A, Murray JA, Kagnoff MF. American Gastroenterological Association (AGA) Institute technical review on the diagnosis and management of celiac disease. *Gastroenterology*. 2006;131(6):1981-2002.
53. Maglio M, Tosco A, Paparo F, et al. Serum and intestinal celiac disease-associated antibodies in children with celiac disease younger than 2 years of age. *J Pediatr Gastroenterol Nutr*. 2010;50(1):43-48.
54. Robert ME. Gluten sensitive enteropathy and other causes of small intestinal lymphocytosis. *Semin Diagn Pathol*. 2005;22(4):284-294.
55. Biesiekierski JR, Newnham ED, Irving PM, et al. Gluten causes gastrointestinal symptoms in subjects without celiac disease: a double-blind randomized placebo-controlled trial. *Am J Gastroenterol*. 2011;106(3):508-514.
56. Wahnschaffe U, Schulzke JD, Zeitl M, Ullrich R. Predictors of clinical response to gluten-free diet in patients diagnosed with diarrhea-predominant irritable bowel syndrome. *Clin Gastroenterol Hepatol*. 2007;5(7):844-850.
57. Verdu EF. Can gluten contribute to irritable bowel syndrome? *Am J Gastroenterol*. 2011;106(3):516-518.
58. Leffler DA, Dennis M, Hyett B, Kelly E, Schuppan D, Kelly CP. Etiologies and predictors of diagnosis in nonresponsive celiac disease. *Clin Gastroenterol Hepatol*. 2007;5(4):445-450.
59. Catassi C, Fasano A. Celiac disease diagnosis: simple rules are better than complicated algorithms. *Am J Med*. 2010;123(8):691-693.
60. Fasano A, Araya M, Bhatnagar S, et al; Celiac Disease Working Group, FISPUGHAN. Federation of International Societies of Pediatric Gastroenterology, Hepatology, and Nutrition consensus report on celiac disease. *J Pediatr Gastroenterol Nutr*. 2008;47(2):214-219.
61. Villalta D, Crovatto M, Stella S, Tonutti E, Tozzoli R, Bizzaro N. False positive reactions for IgA and IgG anti-tissue transglutaminase antibodies in liver cirrhosis are common and method-dependent. *Clin Chim Acta*. 2005;356(1-2):102-109.
62. Peracchi M, Trovato C, Longhi M, et al. Tissue transglutaminase antibodies in patients with end-stage heart failure. *Am J Gastroenterol*. 2002;97(11):2850-2854.
63. Ferrara F, Quaglia S, Caputo I, et al. Anti-transglutaminase antibodies in non-coeliac children suffering from infectious diseases. *Clin Exp Immunol*. 2010;159(2):217-223.
64. Rubio-Tapia A, Murray JA. Classification and management of refractory coeliac disease. *Gut*. 2010;59(4):547-557.
65. West J, Logan RF, Smith CJ, Hubbard RB, Card TR. Malignancy and mortality in people with coeliac disease: population based cohort study. *BMJ*. 2004;329(7468):716-719.
66. Solaymani-Dodaran M, West J, Logan RF. Long-term mortality in people with celiac disease diagnosed in childhood compared with adulthood: a population-based cohort study. *Am J Gastroenterol*. 2007;102(4):864-870.
67. Ludvigsson JF, Montgomery SM, Ekbohm A, Brandt L, Granath F. Small-intestinal histopathology and mortality risk in celiac disease. *JAMA*. 2009;302(11):1171-1178.
68. Evans KE, McAllister R, Sanders DS. Should we screen for coeliac disease? no. *BMJ*. 2009;339:b3674.
69. Fasano A. Should we screen for coeliac disease? yes. *BMJ*. 2009;339:b3592.
70. Strong K, Wald N, Miller A, Alwan A; WHO Consultation Group. Current concepts in screening for noncommunicable disease: World Health Organization Consultation Group Report on methodology of noncommunicable disease screening. *J Med Screen*. 2005;12(1):12-19.
71. Lohi S, Mäki M, Montonen J, et al. Malignancies in cases with screening-

identified evidence of coeliac disease: a long-term population-based cohort study. *Gut*. 2009;58(5):643-647.

72. van Koppen EJ, Schweizer JJ, Csizmadia CG, et al. Long-term health and quality-of-life consequences of mass screening for childhood celiac disease: a 10-year follow-up study. *Pediatrics*. 2009;123(4):e582-e588.
73. Johnston SD, Rodgers C, Watson RG. Quality of life in screen-detected and typical coeliac disease and the effect of excluding dietary gluten. *Eur J Gastroenterol Hepatol*. 2004;16(12):1281-1286.
74. Mustalahti K, Lohiniemi S, Collin P, Vuolteenaho N, Laippala P, Mäki M. Gluten-free diet and quality of life in patients with screen-detected celiac disease. *Eff Clin Pract*. 2002;5(3):105-113.
75. Virta LJ, Kaukinen K, Collin P. Incidence and prevalence of diagnosed coeliac disease in Finland: results of effective case finding in adults. *Scand J Gastroenterol*. 2009;44(8):933-938.
76. Lee AR, Ng DL, Zivin J, Green PH. Economic burden of a gluten-free diet. *J Hum Nutr Diet*. 2007;20(5):423-430.
77. Thompson T, Dennis M, Higgins LA, Lee AR, Sharrett MK. Gluten-free diet survey: are Americans with coeliac disease consuming recommended amounts of fibre, iron, calcium and grain foods? *J Hum Nutr Diet*. 2005;18(3):163-169.
78. Kinsey L, Burden ST, Bannerman E. A dietary survey to determine if patients with coeliac disease are meeting current healthy eating guidelines and how their diet compares to that of the British general population. *Eur J Clin Nutr*. 2008;62(11):1333-1342.
79. Whitaker JK, West J, Holmes GK, Logan RF. Patient perceptions of the burden of coeliac disease and its treatment in the UK. *Aliment Pharmacol Ther*. 2009;29(10):1131-1136.
80. Zarkadas M, Cranney A, Case S, et al. The impact of a gluten-free diet on adults with coeliac disease: results of a national survey. *J Hum Nutr Diet*. 2006;19(1):41-49.
81. Olsson C, Hörnell A, Ivarsson A, Sydner YM. The everyday life of adolescent coeliacs: issues of importance for compliance with the gluten-free diet. *J Hum Nutr Diet*. 2008;21(4):359-367.
82. Catassi C, Fabiani E, Iacono G, et al. A prospective, double-blind, placebo-controlled trial to establish a safe gluten threshold for patients with celiac disease. *Am J Clin Nutr*. 2007;85(1):160-166.
83. Akobeng AK, Thomas AG. Systematic review: tolerable amount of gluten for people with coeliac disease. *Aliment Pharmacol Ther*. 2008;27(11):1044-1052.
84. Schuppan D, Dennis MD, Kelly CP. Celiac disease: epidemiology, pathogenesis, diagnosis, and nutritional management. *Nutr Clin Care*. 2005;8(2):54-69.
85. Thompson T, Lee AR, Grace T. Gluten contamination of grains, seeds, and flours in the United States: a pilot study. *J Am Diet Assoc*. 2010;110(6):937-940.
86. Hall NJ, Rubin G, Charnock A. Systematic review: adherence to a gluten-free diet in adult patients with coeliac disease. *Aliment Pharmacol Ther*. 2009;30(4):315-330.
87. Leffler DA, Dennis M, Edwards George JB, et al. A simple validated gluten-free diet adherence survey for adults with celiac disease. *Clin Gastroenterol Hepatol*. 2009;7(5):530-536, 536, e1-e2.
88. Abdulkarim AS, Burgart LJ, See J, Murray JA. Etiology of nonresponsive celiac disease: results of a systematic approach. *Am J Gastroenterol*. 2002;97(8):2016-2021.
89. Murray JA, Watson T, Clearman B, Mitros F. Effect of a gluten-free diet on

gastrointestinal symptoms in celiac disease. *Am J Clin Nutr*. 2004;79(4):669-673.

90. NIH Consensus Development Conference on Celiac Disease. *NIH Consens State Sci Statements*. 2004;21(1):1-23.
91. American Dietetic Association. Celiac Disease Evidence-Based Nutrition Practice Guideline. <http://www.adaevidencelibrary.com/topic.cfm?cat=3677>. Accessed April 24, 2011.
92. Primary Care Society for Gastroenterology. *The Management of Adults With Coeliac Disease in Primary Care*. May 2006. http://www.coeliac.org.uk/sites/files/coeliac/PCSG_the_management_of_adults_with_coeliac_disease_in_primary_care.pdf. Accessed May 4, 2011.
93. World Gastroenterology Organisation. World Gastroenterology Organisation Practice Guidelines: Celiac Disease. http://www.worldgastroenterology.org/assets/downloads/en/pdf/guidelines/04_celiac_disease.pdf. Accessed April 24, 2011.
94. Di Sant'Agnes PA. Idiopathic celiac disease, II: course and prognosis. *Pediatrics*. 1953;11(3):224-237.
95. Rubio-Tapia A, Rahim MW, See JA, Lahr BD, Wu TT, Murray JA. Mucosal recovery and mortality in adults with celiac disease after treatment with a gluten-free diet. *Am J Gastroenterol*. 2010;105(6):1412-1420.
96. Green PH, Cellier C. Celiac disease. *N Engl J Med*. 2007;357(17):1731-1743.
97. Schuppan D, Junker Y, Barisani D. Celiac disease: from pathogenesis to novel therapies. *Gastroenterology*. 2009;137(6):1912-1933.
98. Tursi A, Giorgetti G, Brandimarte G, Elisei W. Effect of gluten-free diet on pregnancy outcome in celiac disease patients with recurrent miscarriages. *Dig Dis Sci*. 2008;53(11):2925-2928.
99. Tata LJ, Card TR, Logan RF, Hubbard RB, Smith CJ, West J. Fertility and pregnancy-related events in women with celiac disease: a population-based cohort study. *Gastroenterology*. 2005;128(4):849-855.
100. Ludvigsson JF, Montgomery SM, Ekbohm A. Celiac disease and risk of adverse fetal outcome: a population-based cohort study. *Gastroenterology*. 2005;129(2):454-463.
101. Soni S, Badawy SZ. Celiac disease and its effect on human reproduction: a review. *J Reprod Med*. 2010;55(1-2):3-8.
102. Lanzini A, Lanzarotto F, Villanacci V, et al. Complete recovery of intestinal mucosa occurs very rarely in adult coeliac patients despite adherence to gluten-free diet. *Aliment Pharmacol Ther*. 2009;29(12):1299-1308.
103. Hernandez L, Green PH. Extraintestinal manifestations of celiac disease. *Curr Gastroenterol Rep*. 2006;8(5):383-389.
104. Bernstein CN, Leslie WD, Leboff MS. AGA technical review on osteoporosis in gastrointestinal diseases. *Gastroenterology*. 2003;124(3):795-841.
105. Hadjivassiliou M, Sanders DS, Grünewald RA, Woodroffe N, Boscolo S, Aeschlimann D. Gluten sensitivity: from gut to brain. *Lancet Neurol*. 2010;9(3):318-330.
106. Cosnes J, Cellier C, Viola S, et al; Groupe D'Etude et de Recherche Sur la Maladie Coeliaque. Incidence of autoimmune diseases in celiac disease: protective effect of the gluten-free diet. *Clin Gastroenterol Hepatol*. 2008;6(7):753-758.
107. Leffler DA, Edwards George JB, Dennis M, Cook EF, Schuppan D, Kelly CP. A prospective comparative study of 5 measures of gluten-free diet adherence in adults with coeliac disease. *Aliment Pharmacol Ther*. 2007;26(9):1227-1235.
108. Dipper CR, Maitra S, Thomas R, et al. Anti-tissue transglutaminase antibodies in the follow-up of adult coeliac disease. *Aliment Pharmacol Ther*. 2009;30(3):236-244.