Celiac Disease Diagnosis and Management
A 46-Year-Old Woman With Anemia

Daniel Leffler, MD, MS, Discussant

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.
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 system 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,
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.3

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 diagnosis47,48 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 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, 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, 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, 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, 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, but the positive predictive value in moderate-risk groups is less than 30%, precluding efficient diagnosis (A).2
Negative serologic test result may not adequately rule out celiac disease (B). Although tTG IgA testing is generally accepted to be the initial test of choice for celiac disease in most situations, 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). 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. To confirm the diagnosis of celiac disease, patients with intestinal damage

| Table 1. Presenting Signs and Symptoms and Pretest Probability of Celiac Diseasea |
|-----------------------------------------------|-----------------|------------------|-----------------|-----------------|
| **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. | Risk of celiac disease in first- and second-degree relatives is approximately 8% and 4%, respectively, and increases to 20% in symptomatic family members. | 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. | Two separate studies of cost-effectiveness of celiac testing in irritable bowel syndrome concluded that testing is generally warranted in this population. | 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. |
| **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. | 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%. |

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Celiac disease is rare in individuals of pure East Asian, Southeast Asian, sub-Saharan African, and Inuit descent. Recommendations do not apply to these groups. The 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 cirrhosis52 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,66,67 mortality rates may be persistently elevated68 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.69 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).32

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).32,60 Fortunately, although diagnosis is often markedly delayed,57,60 studies suggest that with proper clinician education, case finding can be highly effective.65

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.32 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). 

In adults, testing is reserved for those with signs or symptoms suggestive of celiac disease (C), 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 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. 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).

**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. 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, 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. 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.

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) and to make matters worse, gluten is a ubiquitous ingredient/contaminant in many foods and even medications. 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 and is associated with a lax attitude toward gluten exposure, and even inadvertent gluten exposure commonly results in recurrent symptoms.

For clinically evident celiac disease, evidence exists for the beneficial effect of a gluten-free diet on symptoms and quality of life, 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). However, as discussed in the section on screening, limited data suggest that asymptomatic patients may safely continue a regular diet with proper monitoring, 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.

**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% to one with a very modestly increased standardized mortality rate of 1.39 (95% CI, 1.33-1.45). 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, 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. Advances in diagnosis have propelled celiac disease from an uncommon disorder to one of the most common and most rapidly increas-

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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).\(^9\)\(^8\)\(^9\) 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 induction of immune tolerance through “vaccination” with gluten peptides, among other possibilities (FIGURE 3).\(^9\)\(^7\) 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).\(^9\)\(^8\)\(^9\) 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).\(^9\)\(^2\)\(^9\) Because of the high prevalence of nutritional deficiencies, I

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

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Abbreviation: Ttg, tissue transglutaminase.

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\(^b\)Guidelines referenced are the most recently published. All guidelines apply to both adults and children unless otherwise specified.

\(^c\)Recommended in Rostom et al.\(^2\)\(^2\)

\(^d\)Recommended in Hill et al.\(^2\)\(^3\)

\(^e\)Recommended by the National Institutes of Health Consensus Development Conference on Celiac Disease.\(^9\)\(^3\)

\(^f\)Recommended by the American Dietetic Association.\(^9\)\(^1\)

\(^g\)Recommended by the Primary Care Society for Gastroenterology.\(^9\)\(^2\)

\(^h\)Recommended by the World Gastroenterology Organisation.\(^9\)\(^0\)
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 osteo-
penia, 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 auto-
immunity (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 sympto-
matic 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 approxi-
mately 1 year after adoption of a gluten-free diet. After-
ward, visits for celiac disease can be continued on an
annual basis with both a dietitian and a physician knowl-
edgeable about celiac disease.

QUESTIONS AND DISCUSSION

MS J: Could my miscarriages have been related to celiac dis-
ease?

DR LEFFLER: Currently, the typical new diagnosis of ce-
liac 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 inflam-
mmatory consequences on fertility27,100 the reproductive life
of many patients is irreversibly affected (B). In particular,
the risk of miscarriage appears higher in women with un-
treated celiac disease compared with the general popula-
tion (C).101 For these reasons, clinicians should maintain a
very low threshold for celiac disease testing in this popu-
lation.

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 indi-
viduals with long-standing, severe celiac enteropathy can
expect to achieve complete or near complete intestinal heal-
ning with gluten avoidance and nutritional support, al-
though 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 ad-
hherence (B).93,102

Outside of the intestine, however, healing is not always
 ensured. A number of extraintestinal manifestations of ce-
Celiac 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). One of the most common associations with celiac disease is reduced BMD, which is seen in more than half of patients at diagnosis. 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). 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). 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).

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. 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). No matter why people choose to follow a gluten-free diet, given nutritional concerns including lack of fiber and B vitamins, 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). 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). However, lacking more sensitive noninvasive tests of intestinal health, it is still recommended to repeat tTG IgA measurements on a yearly basis, and a decrease in serologic titer during the first year of treatment is associated with gluten avoidance (B). A persistently positive test result should prompt evaluation for a number of potential issues, the most common being gluten exposure.

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.

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. 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, 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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