Screening for celiac disease in average-risk and high-risk populations

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***Abstract*:** The prevalence of celiac disease is rising. As a result there is increasing interest in the associated mortality and morbidity of the disease. Screening of asymptomatic individuals in the general population is not currently recommended; instead, a strategy of case finding is the preferred approach, taking into account the myriad modes of presentation of celiac disease. Although a gluten-free diet is the treatment of choice in symptomatic patients with celiac disease, there is no consensus on whether institution of a gluten-free diet will improve the quality of life in asymptomatic screen-detected celiac disease patients. A review of the studies that have been performed on this subject is presented. Certain patient groups such as those with autoimmune diseases may be offered screening in the context of an informed discussion regarding the potential benefits, with the caveat that the data on this issue are sparse. Active case finding seems to be the most prudent option in most clinical situations.

***Keywords*:** Celiac disease, mass screening, quality of life

Introduction

Celiac disease is common, with a prevalence of nearly 1% in Western populations, including the United States [Rubio-Tapia *et al.* 2009; Bingley *et al.* 2004; Fasano *et al.* 2003; Maki *et al.* 2003]. The prevalence has risen significantly in the past 50 years with one study from the United States finding a fourfold increase in the prevalence, with another study from Finland reporting a twofold increase [Rubio-Tapia *et al.* 2009; Lohi *et al.* 2007]. The increased risks of malignancy and mortality are reduced in the years subsequent to diagnosis, suggesting that adherence to a gluten-free diet may nullify or reduce this increased risk. Most of the risk for malignancy occurs before the diagnosis of celiac disease although the risk of non-Hodgkin's lymphoma seems to persist despite the gluten-free diet [Green *et al.* 2003]. There is a reported increased mortality in patients with celiac disease, mainly due to cardiovascular disease and malignancy [Ludvigsson *et al.* 2009]. Patients on a gluten-free diet have shown clinical improvement and exposure to gluten may be a factor contributing to the development of a secondary form of refractory celiac disease [Cellier *et al.* 2000]. However, the gluten-free diet can pose considerable psychological and social burden on the patient, given its difficulty and expense [Whitaker *et al.* 2009; Lee *et al.* 2007; Sverker *et al.* 2005; Hallert *et al.* 2003].

The institution of the gluten-free diet is clearly indicated in symptomatic patients who present with classical symptoms such as diarrhea, or 'atypical' symptoms such as anemia or osteoporosis. The gluten-free diet has been proven to be effective in a majority of patients with celiac disease with regards to controlling both symptoms and normalization of lab abnormalities [Green and Cellier, 2007]. However, it is less clear that asymptomatic individuals without laboratory abnormalities would benefit from diagnosis and treatment [Ukkola *et al.* 2011; Tontini *et al.* 2010; Nachman *et al.* 2009; van Koppen *et al.* 2009; Whitaker *et al.* 2009; Viljamaa *et al.* 2005; Johnston *et al.* 2004; Mustalahti *et al.* 2002]. In this article, we review the literature and highlight recent studies that have addressed the issue of how screening asymptomatic patients and prescribing a gluten-free diet affects quality of life.

Mortality in celiac disease

Patients with undiagnosed celiac disease have been shown to have a higher mortality rate than those with negative serologies for celiac disease [Rubio-Tapia *et al.* 2009; Metzger *et al.* 2006]. Patients diagnosed with celiac disease also have

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increased mortality rates [West *et al.* 2004; Corrao *et al.* 2001]. One Swedish study showed a modestly increased risk of death in both children and adults who were diagnosed with celiac disease, the risk decreasing with time, but still significant after 5 years of diagnosis. This study also showed that those patients with positive celiac disease antibodies but normal intestinal biopsy were also at increased risk of death [Ludvigsson *et al.* 2009]. Such patients are assumed by some to be healthy and are often not prescribed a gluten-free diet; these patients fall under the spectrum of 'gluten sensitivity' [Green, 2009].

Screening for celiac disease: general considerations

In 1968, the World Health Organization issued guidelines for determining whether a disease is appropriate for mass screening [Wilson and Jungner, 1968]. Whether celiac disease confirms to the criteria for screening or not is a matter of debate.

A minority view maintains the belief that the general population should undergo screening for celiac disease because it fulfills the major criteria for mass screening: difficulty in early detection, a high prevalence, availability of sensitive and specific tests, and available treatment, while delay in treatment can lead to complications [Fasano, 2009].

It remains unclear whether screening programs targeting the general population will identify symptomatic or asymptomatic individuals. In a prospective screening program implemented in Spain, screen-detected individuals had high rates of abdominal pain and diarrhea [Marine *et al.* 2009]. In contrast, in a recent screening program in the United States, patients diagnosed with celiac disease were no more likely than those with negative screening results to have gastrointestinal symptoms [Katz *et al.* 2011].

As mentioned above, celiac disease has a prevalence of nearly 1% in the US and Europe. However, diagnosed cases of celiac disease only has a prevalence of about 0.27% or even less [Murray *et al.* 2003; Collin *et al.* 1997; Talley *et al.* 1994]. Since the clinical spectrum is wide and varying, it is very difficult to diagnose celiac disease early in all patients [Green, 2005]. Antibodies to tissue transglutaminase and deamidated gliadin peptide have high sensitivities and specificities and can be used for screening [Sugai *et al.* 2006; Dieterich *et al.* 1998]. There is increased risk of complications in untreated celiac disease patients which include malignancy and severe malabsorption. Studies have found an increased risk of mortality in celiac disease which decreases with appropriate treatment [Rubio-Tapia *et al.* 2009; Corrao *et al.* 2001; Collin *et al.* 1994]. However, one study did not find any increase in mortality [Lohi *et al.* 2009].

Arguments against screening the general population for celiac disease include unacceptably low positive predictive values of current serological tests, given the pretest prevalence of less than 1%. By definition, the positive predictive value (PPV) of a diagnostic test differs in populations with differing risks for celiac disease [Sugai *et al.* 2010]. One recent review of serological evaluations found that the PPV of tissue transglutaminase (tTG) IgA was 72%, assuming a pretest probability of 5% [Leffler and Schuppan, 2010]. Toftedal and colleagues recently concluded that anti-tissue transglutaminase (anti-tTG) concentration at initial serological screening is highly informative in relation to anti-endomysial antibody positivity, number of additional celiac disease-specific antibodies and PPV [Toftedal *et al.* 2010]. Other arguments against screening include poor understanding of natural course of the disease; the challenge of maintaining adherence to a gluten-free diet; conflicting mortality data regarding undiagnosed celiac disease [Lohi *et al.* 2009; Rubio-Tapia *et al.* 2009] and lack of data regarding cost-effectiveness [Evans *et al.* 2009; Collin, 2005]. The general consensus is that there are insufficient data to justify screening for celiac disease in the general population at this time; this was the view put forth in 2004 by the National Institutes of Health consensus development program on celiac disease [NIH, 2004].

Data for cost-effectiveness analysis for screening of celiac disease in various populations are sparse. Yagil and recommended clinical follow up for low risk populations and anti-endomysial antibody testing for high risk population, which, if positive, should be followed by small bowel biopsy [Yagil *et al.* 2005]. Shamir and colleagues reported that mass screening for celiac disease is cost effective in populations with high prevalence, though their recommendation was after some assumptions [Shamir *et al.* 2006]. In a study done in the US, Dorn and Matchar found tTG to be the least costly strategy, which can be combined with endoscopic

biopsy either directly or after human leukocyte antigen (HLA) DQ2/8 screening in patients with low pre-test probability of celiac disease. These authors recommended that the cost of endoscopy should be weighed against consequences of a false positive diagnosis as the pre-test probability increases [Dorn and Matchar, 2008]. In the most recent study on this issue, performed in Israel, Hershcovici and colleagues reported that mass screening for celiac disease is a cost-effective strategy and is associated with improved quality-adjusted life years. However, these authors postulated that heightened awareness of health professionals might be a valid alternative to screening [Hershcovici *et al.* 2010].

High-prevalence groups

In contrast to the general population, screening in high-prevalence groups may prove to have a favorable cost–benefit ratio. In such populations, such as first-degree relatives of patients with celiac disease, patients with type 1 diabetes, autoimmune thyroid disease, and autoimmune liver disease, the greater underlying prevalence of celiac disease will result in fewer false-positive serologic results [Volta *et al.* 2002; Aktay *et al.* 2001; Cuoco *et al.* 1999; Cronin *et al.* 1997].

Argument for screening: amelioration/ prevention of autoimmune disease

The relationship between treating celiac disease and the prevention of autoimmune disease remains controversial. Several studies have found that in patients with type 1 diabetes mellitus and other autoimmune diseases, the diagnosis of celiac disease and subsequent adherence to a gluten-free diet may prevent the development of other autoimmune diseases. Ventura and colleagues reported that prevalence of autoimmune diseases in celiac disease is dependent on the duration of gluten exposure and the auto-antibodies for diabetes and thyroid disease tend to disappear on a gluten-free diet, suggesting that early diagnosis (at a young age) prevents the development of autoimmune diseases [Ventura *et al.* 2000, 1999]. Another group demonstrated that first-degree relatives of celiac disease patients have a higher risk of autoimmune diseases [Cataldo and Marino, 2003]. These studies suggest that screening for celiac disease in relatives may prevent this increased incidence of autoimmune disease.

Collin reported that the risk of celiac disease in various autoimmune diseases is approximately 5% and proposed that increased alertness instead of mass screening should be the strategy for diagnosing celiac disease [Collin, 2005]. Autoimmune disorders may improve on the gluten-free diet when concomitant celiac disease is present [Chin *et al.* 2003; Usai *et al.* 1989]. In addition, Cosnes and colleagues showed that in those diagnosed with celiac disease, a gluten-free diet was protective from developing more autoimmune diseases [Cosnes *et al.* 2008]. Multiple studies have reported clinical improvement in type 1 diabetics who have celiac disease when put on a gluten-free diet [Narula *et al.* 2009; Hansen *et al.* 2006; Amin *et al.* 2002]. Patients with severe liver disease and undiagnosed celiac disease may also benefit from a gluten-free diet; in one case series, diagnosis and treatment with the gluten-free diet was associated with improvement resulting in removal from the transplant list [Kaukinen *et al.* 2002].

However, not all studies have demonstrated that the gluten-free diet is associated with a reduction in risk of autoimmune diseases in patients with celiac disease. Sategna Guidetti and colleagues found no such correlation between gluten exposure and prevalence of autoimmune disorders in patients with late celiac disease diagnosis. These authors did not find any protective role of gluten-free diet in decreasing the prevalence of autoimmune disorders in such patients [Sategna Guidetti *et al.* 2001]. The prevalence of elevated auto-antibodies (against thyroid, pancreas and adrenal) is greater among newly diagnosed patients with celiac disease than those on a gluten-free diet [Toscano *et al.* 2000]. The significance of these elevated auto-antibodies is unknown. Hence, data are conflicting whether early diagnosis of celiac disease reduces incidence of autoimmune diseases.

Argument for screening: decreasing the risk of malignancy

The prevention of celiac disease-related malignancy has been cited as a justification for screening the general population for celiac disease [Fasano, 2009]. While screening the general population is not recommended by any major guidelines, this argument could also be made to justify screening groups with a high prevalence of celiac disease.

In early studies, the risk of developing enteropathy-associated T-cell lymphoma (EATL) was thought to be 40–100 times higher in celiac disease patients than general population [Swinson *et al.*

1983; Cooper *et al.* 1982; Holmes *et al.* 1976]. The risk has been shown to be much lower in patients who are on a strict gluten-free diet [Holmes *et al.* 1989]. However, larger studies have found that the increased risk of lymphoproliferative malignancy in celiac disease patients is more modest than previously thought [Goldacre *et al.* 2008; Anderson *et al.* 2007; West *et al.* 2004]. The reasons for this can be longer dietary treatments, or the fact that these studies studied the risk of any lymphoproliferative malignancy compared with EATL alone [Logan, 2009]. In one study with a large population, EATL was found in only one detected celiac disease patient [Johnston and Watson, 2000]. Another study has found a very high relative risk of small intestinal lymphoma in celiac disease patients. However, even in this study, most cases occurred within 2 years before or after diagnosis of celiac disease [Card *et al.* 2004].

The risk of other malignancies such as cancers of oropharynx and esophagus, and intestinal adenocarcinomas has also been found to be elevated, but it is not clear whether the gluten-free diet will decrease these complications. The risk for malignancies outside the gastrointestinal system has also been reported to be increased [Goldacre *et al.* 2008; Anderson *et al.* 2007; Smedby *et al.* 2005; West *et al.* 2004]. Although the risk for non-Hodgkin lymphomas has been shown to be increased in some studies, the increased risk was only found in patients who were already diagnosed with celiac disease [Mearin *et al.* 2006; Farre *et al.* 2004; Catassi *et al.* 2002].

Askling and colleagues performed a large-scale nationwide study in Swedish population that found that total cancer occurrence is indeed elevated in those patients who were hospitalized for celiac disease or dermatitis herpetiformis. However, this risk was only temporarily increased and not increased after 10 years or so from the initial hospitalization. We agree with the authors' conclusion that the risk for malignant lymphomas and gastrointestinal malignancies may be lower than previously thought [Askling *et al.* 2002].

Two studies show an increased risk of papillary thyroid cancer in patients with celiac disease [Kent *et al.* 2006; Volta *et al.* 2011]; the gluten-free diet did not appear to be protective as most patients were already on the diet at the time of diagnosis of the cancer. The fact that the patients were diagnosed with celiac disease, and under medical care, may be responsible for the increased detection of this malignancy.

Argument against screening: low adherence to the gluten-free diet

Adherence to a gluten-free diet is highly variable (see Table 1). Screening asymptomatic individuals in a high-prevalence group will result in an increasingly common scenario: the prescription of a diet that is expensive and logistically difficult in a patient who feels no apparent ill effect of a regular diet, especially in the US where access to gluten-free products is expensive or logistically difficult. As such, adherence to the gluten-free diet might be low in screen-detected patients. In fact, adherence to a strict gluten-free diet has been found to be low even in symptomatic patients in early studies [Mayer *et al.* 1991; Bardella *et al.* 1994]. In asymptomatic patients diagnosed only by serology, adherence was found to be low [Shamir *et al.* 2007; Fabiani *et al.* 2000]. Some recent studies, though, have reported high adherence rates in screen-detected patients [Ukkola *et al.* 2011; van Koppen *et al.* 2009; Viljamaa *et al.* 2005]. The issue of adherence is crucial in the consideration of whether screening is appropriate, because a low rate of adherence will offset any advantages of screening. A novel seven-item instrument has been developed that helps in evaluating adherence to a gluten-free diet and has been shown to be superior to tissue transglutaminase serology for this purpose [Leffler *et al.* 2009].

Impact on quality of life

The effect of the celiac disease diagnosis on the quality of life in asymptomatic individuals has received relatively little study (see Table 2). One of the first studies in regards to quality of life in 14 asymptomatic screen-detected patients was performed by Mustalahti and colleagues. This study was performed in Finland using psychological and symptom-related questionnaires to assess quality of life. The authors concluded that both symptoms and quality of life improved after institution of gluten-free diet in screen-detected patients. The adherence to gluten-free diet among these patients was also very good [Mustalahti *et al.* 2002]. Another study from Finland on 32 patients using the same questionnaires and Short Form-36 performed in 2005 reported similar findings. The authors postulated that screening is reasonable in high-risk groups because they found that quality of life was comparable to the general population in screen-detected patients. To the best of the authors'

Table 1. Adherence to the gluten-free diet in patients with celiac disease.

Study	Country	Number of patients	Population	Measurement method	Findings		
					Strictly adherent to gluten-free diet	adherent with occasional intake of gluten	Nonadherent (i.e. regular gluten-containing diet)
Mayer *et al.* [1991]	United Kingdom	123	Symptom detected	Precoded questionnaire to patients	65%	11.40%	23.60%
Bardella *et al.* [1994]	Italy	128	Symptom detected	Dietary interview of both patients and their parents	45%	18%	37%
Fabiani *et al.* [2000]	Italy	44	22 Screen detected	Food frequency questionnaire	23%	54%	23%
			22 Symptom detected		68	32	0
Shamir *et al.* [2007]	Israel	51	Screen detected	Telephone interview	8%	92% (no distinction whether occasional or routine gluten intake)	
Viljamaa *et al.* [2005]	Finland	97	53 Screen detected	Interview, 4 day food record, serology	83%	14%	4%
			44 Symptom detected		77%	23%	0%
Ukkola *et al.* [2011]	Finland	698	146 Screen detected	Mailed questionnaire	91%	9%	0%
			552 Symptom detected		84.2%	15.4%	0.4%
Leffler *et al.* [2009]	United States	200	Mixed population	Standardized Dietician evaluation/	74.6%	25.4%	

knowledge, this is the study with the maximum number of asymptomatic screen-detected patients to date [Viljamaa *et al.* 2005]. A study done in 2010 in Italy using Short Form-36 concluded that the quality of life improved in all subgroups of celiac disease patients after commencing the gluten-free diet. However, the number of truly asymptomatic screen-detected patients in this study was very small [Tontini *et al.* 2010].

In a recently reported randomized clinical trial, asymptomatic screen-detected relatives of patients with celiac disease were randomized to either a gluten-free diet or a regular diet. Those randomized to the gluten-free diet had improvements of both the Gastrointestinal Symptom Rating Scale and the Psychological General Well Being score, whereas those randomized to the regular diet had no change. The magnitude and clinical significance of these improvements are not clear [Kurppa *et al.* 2011].

Several of these studies were performed in Finland where there is a high rate of celiac disease diagnosis and subsequent availability of gluten-free foods, which are subsidized by the government. The applicability of these studies to other countries such as the United States where there is a low rate of diagnosis and awareness of celiac disease is unclear.

In contrast to the Finnish studies, studies performed in the United Kingdom have found decreased quality of life scores after prescription of a gluten-free diet in asymptomatic screen-detected patients. One study performed in 2004 using Short Form-36 reported no significant

Table 2. Studies evaluating the quality of life in asymptomatic individuals with screen detected celiac disease.

Reference	Year	Country	Quality of life scale used	Total number of screen-detected patients	Number of *asymptomatic* screen-detected patients	Outcomes/results
Ukkola *et al.* [2011]	2011	Finland	PGWB	146	23	Decreased QOL score in screen-detected patients and improved score in typical symptom-detected patients after 1 year of gluten-free diet.
Tontini *et al.* [2010]	2010	Italy	SF-36	28	3	Improved QOL score after 1 year of gluten-free diet in all subsets whether symptomatic or screen-detected disease patients.
Nachman *et al.* [2009]	2009	Argentina	SF-36, GSRS, BDI	35	10	Improvement in scores on 1 year of gluten-free diet seen in typical symptom-detected patients. Scores both at baseline and after 1 year of gluten free diet in asymptomatic screen-detected patients remained comparable to healthy controls.
van Koppen *et al.* [2009]	2009	Netherlands	DUX – 25, CDDUX	32	20	Improvement in scores on 1 year of gluten free diet seen in typical symptom-detected patients. Scores both at baseline and after 1 year of gluten free diet in asymptomatic screen-detected patients remained comparable to healthy controls.
Whitaker *et al.* [2009]	2009	United Kingdom	Author developed questionnaire	51	19	Two thirds of the typical symptom-detected patients wished to have been diagnosed earlier compared to less than half of asymptomatic screen-detected patients. A quarter of the asymptomatic screen-detected patients regretted being diagnosed.
Viljamaa *et al.* [2005]	2005	Finland	PGWB, GSRS, SF-36	53	32	QOL scores were similar in both typical symptom-detected and asymptomatic screen-detected patients.
Johnston *et al.* [2004]	2004	United Kingdom	SF-36	14	Not specified	Improvement in scores on 1 year of gluten-free diet seen in typical symptom-detected patients. Scores both at baseline and after 1 year of gluten-free diet in asymptomatic screen-detected patients remained comparable to healthy controls.
Mustalahti *et al.* [2002]	2002	Finland	PGWB, GSRS	19	14	Improved QOL score after 1 year of gluten-free diet in all subsets whether typical or screen-detected disease patients.

PGWB, Psychological General Well being; QOL, quality of life; SF-36, Short Form-36 Health Survey; GSRS, Gastrointestinal Symptom Rating Scale; BDI, Beck Depression Inventory; CDDUX, Celiac Disease DUX.

differences between screen-detected patients and healthy controls at baseline or after 1 year of gluten-free diet in terms of quality of life [Johnston *et al.* 2004]. Another study performed in 2009 which used a novel questionnaire developed by the study authors found that gluten-free diet is unacceptable in screen-detected patients. In this study, a quarter of the screen-detected

patients regretted being diagnosed with the disease [Whitaker *et al.* 2009].

A study done in Argentina in 2009 found no significant impact on screen-detected individuals who were prescribed a gluten-free diet. The authors found that the baseline scores in screen-detected patients were better than those with symptoms, and the scores did not improve on institution of gluten-free diet in the former subgroup [Nachman *et al.* 2009].

In a recent study, investigators in Finland identified 23 asymptomatic screen-detected individuals and administered quality of life questionnaires at the time of diagnosis and1 year later. These investigators found that quality of life deteriorated in screen-detected patients after diagnosis and did not improve with a gluten-free diet. This was the opposite of what was seen in people who had symptoms prior to diagnosis. The authors recommended active case finding instead of unselected mass screening for celiac disease [Ukkola *et al.* 2011].

Most studies evaluating quality of life in celiac disease patients have studied adults as subjects, but celiac disease affects the health-related quality of life in children as well [van Doorn *et al.* 2008]. A prospective 10-year study performed in children in the Netherlands in 2008 found no differences in quality of life between asymptomatic screen-detected patients and general population. This study utilized a version of the DUX-25, a generic 25-item questionnaire which measures children's and adolescent's affective evaluation of their daily functioning [Koopman *et al.* 1998]. The CDDUX is a 12-item celiac disease-specific questionnaire which has three subscales comprising 'communication', 'diet', and 'having celiac disease' [van Doorn *et al.* 2008]. The investigators did not find any improvement in these scores after 1 year of the gluten-free diet. The authors recommended starting limited screening and assessing the cost–benefit ratios, before coming to a final conclusion regarding mass screening. They proposed that screen-detected patients should be followed closely and a gluten-free diet should be started only in those who develop symptoms [van Koppen *et al.* 2009].

Thus, the aggregate of evidence at this time supports the notion that diagnosing asymptomatic individuals with celiac disease does not definitively result in improved quality of life. The effect of celiac disease diagnosis on quality of life in asymptomatic patients has not been measured in the United States, where access to gluten-free food remains difficult, and knowledge deficits regarding gluten in the general population remain high [Simpson *et al.* 2011].

Guidelines

The National Institutes of Health 2004 consensus development program on celiac disease recommends that there is currently insufficient evidence to recommend screening for celiac disease in the general population [James, 2005]. For asymptomatic individuals in a group with an increased prevalence of celiac disease, the program states, 'Because current data do not indicate a clear outcome benefit for early detection and treatment of asymptomatic individuals in these groups, routine screening cannot be recommended at this time, but individual discussions regarding the benefits and consequences of testing are warranted'.

Guidelines issued by the American Gastroenterological Association do not recommend screening even in high-risk groups and state that such patients should be tested for celiac disease only if typical or atypical symptoms develop [Rostom *et al.* 2006]. In contrast, guidelines from the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition recommend screening of high-risk groups for celiac disease, and repeat screening at intervals asymptomatic high-risk patients who have negative serology results [Hill *et al.* 2005].

An effective alternative to screening is active case finding in symptomatic individuals. In the general population, this approach has led to the diagnosis of a large number of patients and should be the recommended practice [Virta *et al.* 2009; Catassi *et al.* 2007].

Conclusion

Presently, there are insufficient data to demonstrate that screening the general population or asymptomatic individuals in high-prevalence groups definitively results in clinical benefit. We recommend screening for celiac disease in pediatric and adult patients with certain autoimmune diseases (including autoimmune thyroid disease, autoimmune liver disease, primary biliary cirrhosis and type 1 diabetes mellitus), given the evidence suggesting that treatment with a gluten-free diet

may ameliorate the autoimmune disease and possibly prevent the development of other autoimmune diseases [Ventura *et al.* 2000]. For children and adults who are first-degree relatives of patients with celiac disease and for patients with Down's or Turner's syndrome, we recommend aggressive case finding and maintaining a low threshold for suspicion and screening. If such individuals are asymptomatic, we offer screening to these patients while informing them that the data on this issue are currently sparse. Future studies should focus on practical benefits of diagnosing celiac disease in asymptomatic patients with emphasis on measuring quality of life before and after the diagnosis and introduction of the gluten-free diet.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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