OPINION

# Coeliac disease: to biopsy or not?

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Abstract | Coeliac disease is increasingly recognized as a global problem in both children and adults. Traditionally, the findings of characteristic changes of villous atrophy and increased intraepithelial lymphocytosis identified in duodenal biopsy samples taken during upper gastrointestinal endoscopy have been required for diagnosis. Although biopsies remain advised as necessary for the diagnosis of coeliac disease in adults, European guidelines for children provide a biopsy-sparing diagnostic pathway. This approach has been enabled by the high specificity and sensitivity of serological testing. However, these guidelines are not universally accepted. In this Perspective, we discuss the pros and cons of a biopsy-avoiding pathway for the diagnosis of coeliac disease, especially in this current era of the call for more biopsies, even from the duodenal bulb, in the diagnosis of coeliac disease. In addition, a contrast between paediatric and adult guidelines is presented.

Coeliac disease is common, occurring in ~1% of the general population worldwide[1]. The disease affects both children and adults; however, the bulk of those with the disease remain undiagnosed. Although the clinical manifestations of the condition are tremendously varied, involving both intestinal and extraintestinal symptoms, all patients have a characteristic pathology in the small intestine[1]. These changes include villous atrophy, crypt hypertrophy and intraepithelial lymphocytosis. These pathological changes have been regarded as the gold standard for diagnosing coeliac disease. Originally, the diagnosis was made after the analysis of biopsy samples obtained with the use of peroral suction biopsy capsules or tubes[2,3]. With the advent of modern-day endoscopic techniques, initial studies in the late 1970s demonstrated the adequacy of endoscopic biopsies of the second part of the duodenum[4] and, in 2010, the duodenal bulb[5]. Coeliac serological testing, especially for immunoglobulin A (IgA) antibodies to tissue transglutaminase 2 (anti-TG2) and the endomysial IgA antibody (EMA), has facilitated the identification of patients who then undergo endoscopic biopsy[1]. In 2012, the need for duodenal biopsy was challenged with the publication of the most recent European Society for the Study of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidelines for the diagnosis of coeliac disease[6]. In these guidelines, for the first time, a subset of children was identified as candidates for the diagnosis of coeliac disease without confirmation of villous atrophy by duodenal biopsies.

Previous ESPGHAN guidelines have been readily adopted worldwide by both paediatric and adult gastroenterologists. However, these current guidelines have not been accepted as readily by, for example, paediatric gastroenterologists in the USA or Australia (personal communication, D. Cameron, The Royal Children's Hospital Melbourne, Australia). Adult gastroenterology guidelines all dictate the need for biopsies[7–9]. Interestingly, the ESPGHAN guideline release coincides with quality-of-care studies that have incriminated failure to biopsy the duodenum[10] and an inadequate number of duodenal biopsies[11,12] as reasons for the underdiagnosis of coeliac disease. Follow-up biopsies can also be important in documenting healing in children, as suggested in a retrospective study published in 2017 (REF. 13). Follow-up biopsies are of greatest value when there is an initial, diagnostic biopsy sample that can be used for comparison.

In this Perspective, we present the currently accepted methods of diagnosing coeliac disease in adults and the pros and cons that reflect the adoption of the new paediatric guidelines. The insights given are from paediatric gastroenterologists (N.R.R. and S.H.) and adult-care gastroenterologists (D.S.S. and P.H.R.G.) from both Europe (D.S.S. and S.H.) and the USA (N.R.R. and P.H.R.G.). Once the diagnosis of coeliac disease is established, patients are advised to adopt a gluten-free diet (GFD) and to maintain it for life. This point needs to be emphasized because the adoption of a GFD can be a major disruption to the habits and lifestyles of individual paediatric or adult patients and their entire families, and adopting this diet seems to be a major determinant of the quality of life of those with coeliac disease[13]. Thus, incorrectly or overdiagnosing coeliac disease needs to be avoided.

## Coeliac disease in adults

***Diagnosis.*** A combination of coeliac serology and duodenal biopsies is required for the diagnosis of coeliac disease in adults. The current American College of Gastroenterology[7], British Society of Gastroenterology[8] and UK National Institute for Health and Care Excellence (NICE)[9] guidelines recommend coeliac serological testing of high-risk adults as a guide to who should undergo duodenal biopsies. An anti-TG2 assessment should be performed as a first-line test because of its high sensitivity and negative predictive value, as well as being less expensive than testing for EMA. A study of 2,000 patients with a prevalence of coeliac disease of 3.9% compared the sensitivities of testing for anti-TG2 alone and a two-step approach using tests for anti-TG2 and EMA. Anti-TG2 alone was found to be a more sensitive marker for coeliac disease than anti-TG2 plus EMA (sensitivities of 90.9% versus 85.7% and negative predictive values of 99.6% versus 99.7%)[14]. However, if the anti-TG2 level is just above the upper limit of normal (ULN), EMA should be tested for[8], which has a high specificity of 95%[15,16].

It should be noted that EMA testing utilizes immunofluorescence techniques that use monkey oesophageal or human umbilical tissues as the substrate and they have limited availability. EMA testing is also expensive and labour intensive, and the interpretation of the results is subjective.

A meta-analysis published in 2012 found that the anti-deamidated gliadin peptide antibody (anti-DGP) had a pooled sensitivity ranging from 80.1–98.6%, whereas that of anti-TG2 was ≥90%[17]. Patients with an IgA deficiency do not produce anti-TG2 or EMA and, therefore, could give a false-negative result. An IgA deficiency is ten times more prevalent in patients with coeliac disease than in the general population (2.6% versus 0.14–0.2%)[18]. Thus, it is common to test for total IgA levels in conjunction with coeliac disease serology. For those with an IgA deficiency, the IgG forms of anti-TG2, EMA and anti-DGP can be tested for instead. Most studies of IgA deficiency in the context of coeliac disease have examined selective IgA deficiency (IgA absent or present at values below the level of detection); however, one study examined patients with coeliac disease and subnormal IgA values (partial deficiency)[19]. Most patients with coeliac disease and a partial IgA deficiency do mount an IgA antibody response to TG2 and do not require IgG-based serological testing.

In the past decade, several point-of-care tests for anti-TG2 have become commercially available for purchase by patients in pharmacies and online[20,21]. However, the literature contains fairly limited data on their performance compared with that of conventional serology. Thus, results should be confirmed with anti-TG2 and EMA testing. Moreover, in our experience, it is important to counsel the patient to eat a gluten-containing diet (10 g of gluten a day, equivalent to four slices of bread, is typically advised) for 6 weeks before testing to ensure that serological and histological results are not affected. However, a study published in 2013 suggested that 75% of patients will meet the diagnostic criteria for coeliac disease after a 2-week challenge of only 3 g of gluten[22].

Although determining the presence of an HLA-DQ2 or HLA-DQ8 status is part of the biopsy-sparing algorithm for children, it has little role in the diagnosis of coeliac disease in adults because it is unnecessary when serological and biopsy results confirm the diagnosis. Patients who are difficult to diagnose, such as those with seronegative coeliac disease, are exceptions. In addition, knowledge of HLA status can be useful in excluding individuals from further testing who are at risk of developing coeliac disease if they lack these requisite genetic markers, such as family members. HLA testing is also valuable in the assessment of those who have adopted a GFD and want to find out if they could have coeliac disease. In this setting, serological test results and biopsy findings might be normal; the absence of HLA-DQ2 or HLA-DQ8 precludes a diagnosis of coeliac disease.

***Guidelines for adults: how should the diagnosis of coeliac disease be confirmed?***

Duodenal biopsy samples showing increased intraepithelial lymphocyte levels, crypt hyperplasia and villous atrophy or shortening along with positive coeliac serological results confirm the diagnosis of coeliac disease in both asymptomatic and symptomatic adults. Although the villous structures appear shortened and atrophic when examined using light microscopy, it must be highlighted that the mucosa is hyperplastic, as evidenced by prominent crypt hyperplasia[23]. Coeliac disease can be diagnosed in some centres in the presence of normal villous architecture through the demonstration of anti-TG2 deposits in the submucosa[24]. Patients with positive serological tests and normal biopsies would be classified as having potential coeliac disease[25]. Not all patients with potential coeliac disease develop mucosal flattening during follow-up[26], and some might lose their seropositivity[27]. How many patients with potential coeliac disease who will benefit from a GFD is unclear, although symptomatic adults in a prospective study showed improvement[26], and children with potential coeliac disease, anaemia and iron deficiency[28] improved on a GFD. A more widespread ability to detect antibodies to anti-TG2 in biopsy samples would probably clarify this uncertainty. The recognition of these very early stages of coeliac disease[24], and of seronegative coeliac disease, reflects the complexity and changing nature of the diagnosis of this condition[29].

Although anti-TG2 and EMA tests have been demonstrated to have excellent sensitivities, these sensitivities often drop when the tests are performed in the 'real world', with a low (1%) prevalence in the general population[30]. This decrease in sensitivity suggests that serological results are insufficient for the diagnosis of coeliac disease. Thus, adult-practice guidelines[7–9] still recommend confirmatory duodenal biopsies as mandatory to ensure that patients are correctly diagnosed with coeliac disease before being subjected to a lifelong GFD. Biopsies should incorporate a minimum of four samples from the second part of the duodenum and at least one sample from the duodenal bulb[31]. The diagnostic yield is further improved by using a 'single-bite' technique[32].

However, many investigators have suggested that a 'no-biopsy' approach can be undertaken for adults, with a positive predictive value (PPV) of 100%[33–41]. The investigators achieved this result by adjusting the cut-off level for anti-TG2. For example, in the study by Hill *et al.*[33], an anti-TG2 cut-off value of ten times the ULN range resulted in a 100% PPV. At face value, this approach would seem an entirely reasonable change in clinical practice as patients could be spared an endoscopic procedure. These studies included patients with a confirmed diagnosis of coeliac disease, but when assessments of PPV for anti-TG2 are undertaken in populations with a low prevalence of coeliac disease, the PPV is considerably less[14,42]. Numerous anti-TG2 kits are available; notably, not all test kits perform to the same high standards, rendering divergent results[43]. This inconsistency could lead to clinical uncertainty unless individual laboratories locally validate the test they decide to use; this perspective is supported by studies that have demonstrated a wide variability of the ULNs when comparing different commercially available anti-TG2 assays[44].

There are a number of other reasons to consider duodenal biopsies for adults when a clinician suspects coeliac disease (BOX 1). One reason is that up to 30% of the adults with coeliac disease seen in specialty centres have persistent symptoms following treatment[45]. In that setting, knowledge of the results of biopsies taken at diagnosis is important to ensure that coeliac disease is actually present and that an alternative condition, such as a lymphoma, is not already present. In addition, an elevated anti-TG2 level could represent a false positive because not all the tests have a 100% PPV. Moreover, it has also been documented that both adults and children can have a temporary coeliac or gluten autoimmunity characterized by positive serological test results that eventually normalizes despite the continuance of a regular diet[46]. In this setting, biopsy results can be normal.

## Childhood coeliac disease

***Diagnosis.*** The first guidelines for the diagnosis of coeliac disease were published by ESPGHAN in 1979 (REF. 47), which

Box 1 | **Pros and cons of a biopsy-based diagnosis of coeliac disease**

**Reasons for proceeding with a biopsy**

- Potential for erroneous coeliac disease diagnosis (false-positive or potential coeliac disease) (A, C)
- Patients might take reassurance in having a histological diagnosis (A, C)
- Patients with either IBS or Crohn's disease of the small bowel can report symptom relief by adopting a gluten-free diet (GFD)[86] (A)
- Baseline histological tests can enable the assessment of severity (degree of villous atrophy) and give the patient confidence about histological improvement if future biopsy samples are taken (A)
- Some centres will not prescribe a GFD unless the diagnosis of coeliac disease is proven (A, C)
- Many patients need an upper gastrointestinal endoscopy if they have anaemia or relevant symptoms, such as abdominal pain, to exclude coincidental pathologies such as ulcers or cancer (A, C)
- Patients might have a temporary coeliac or gluten autoimmunity along with a negative biopsy (A, C)
- Comparison of the initial biopsy sample with subsequent biopsies is valuable when patients present with persistent or new symptoms (A, C)
- A gastroscopy is more easily tolerated by adults and does not require a general anaesthetic (A)
- Necessary for the diagnosis of refractory coeliac disease (A)
- To prevent the misuse of no-biopsy diagnostic algorithms (that is, use in asymptomatic patients or the failure to repeat serological tests)

**Reasons for avoiding biopsy**

- General anaesthesia is often required for children and adolescents undergoing endoscopy (C)
- Cost of a no-biopsy diagnosis is generally less given the elimination of procedural and pathology costs (A, C)
- In childhood, gastrointestinal cancers are exceedingly rare and usually would be obvious on the basis of clinical evidence (C)
- Avoidance of procedural risks, such as rare anaesthesia reactions or aspiration pneumonia (A, C)
- Excellent specificity for the diagnosis of coeliac disease when serological, genetic and symptom criteria from guidelines are met (C)

A, pertains to adult populations; C, pertains to children.

recommended that the diagnosis of coeliac disease be based on duodenal biopsies at three occasions: one at symptom onset, one after 1–2 years on a GFD and one after a subsequent gluten challenge. This approach served to clarify the diagnosis in a clinical situation dominated by more aggressive gastrointestinal infections than we see today. These criteria were modified in 1989 and published in 1990 (REF. 48) with the so-called revised ESPGHAN criteria, which restricted the number of biopsies to one at symptom onset, except in infants and children <2 years of age, in whom the three-biopsy series mentioned earlier was still regarded as necessary owing to differential diagnostic concerns, and it included an assessment of the clinical response at follow-up. As mentioned, these guidelines were readily accepted by gastroenterologists in adult care.

Small intestinal biopsies continued to be recommended as the gold standard for diagnosis in children from 2000 to 2010, with other organizations, such as the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition[49], the American Gastroenterological Association[50] and the Federation of International Societies of Pediatric Gastroenterology, Hepatology and Nutrition[51], continuing to recommend a biopsy for confirmation of a coeliac disease diagnosis.

During the past few decades, the quality of serological testing for coeliac disease has increased, and this development has led to the suggestion that a diagnosis of coeliac disease can be made on the basis of sequential serological tests. Serological testing is commonly referred to as 'screening for coeliac disease', and a prerequisite for omitting a histological analysis of duodenal biopsies was suggested with antibody levels or titres above a certain cut-off point[33]. In this study published in 2008 (REF. 33), the authors suggested, on the basis of a rather small number of adult patients ($n = 146$), that such a cut-off level was, conveniently, ten times the ULN of the assay. The observation that positive serological results accurately reflect the enteropathy of the duodenal mucosa and, therefore, might enable the substitution of a histological analysis of biopsy samples with serological testing has been confirmed in several reports[35,52]. These reports were taken into account in the 2012 ESPGHAN guidelines for the diagnosis of coeliac disease[6]. The ESPGHAN guidelines gave recommendations as to the interpretation of tests, including the histological analysis of duodenal biopsies, and were accompanied by an evidence report evaluating the evidence base for serological diagnostic tools[18]. A similar algorithm for children as in the ESPGHAN guidelines was later published by the British Society of Paediatric Gastroenterology, Hepatology and Nutrition (BSPGHAN) and Coeliac UK[53].

The 2012 ESPGHAN guidelines recommend that the first step in the diagnosis of coeliac disease in children be based on patient history and signs and on the determination of anti-TG2 levels, with a positive result leading to referral to a paediatric gastroenterologist (FIG. 1). If the anti-TG2 test is positive, but the level is <10 times the ULN, an upper endoscopy with multiple duodenal biopsies, including of the duodenal bulb, is recommended. If the patient is distinctly symptomatic, particularly with symptoms of malabsorption, and the anti-TG2 level is >10 times above the ULN of the particular assay, the option will be discussed with the patient and family to make an eventual diagnosis of coeliac disease on the basis of further testing, without duodenal biopsies and histological analysis. This approach includes a second blood sample to re-measure anti-TG2 levels, along with testing of EMA and of HLA-DQ2 and HLA-DQ8 status. If the patient has a low IgA level or an IgA deficiency, IgG-based tests can be used. If the anti-TG2 test is still positive and >10 times the ULN, the EMA test is positive and HLA-DQ2 or HLA-DQ8 is present, a diagnosis of coeliac disease can be made. If the patient and family prefer an endoscopy with histological analysis of duodenal biopsies, this approach could also lead to a diagnosis of coeliac disease.

***Advantages of a no-biopsy coeliac disease diagnosis for children.*** There are pitfalls in the interpretation of duodenal biopsies. Although the histological analysis of duodenal biopsy samples in coeliac disease has been used as a gold standard in practically all studies, it might not always qualify as a reference standard because histological analyses have been reported to lack diagnostic accuracy owing

to high variability between observers[54,55], differences between routine and more specialized pathology labs[56], low rates of the correct orientation of biopsy samples[54] and possible inadequacies in histological analysis[57,58]. In a large multicentre European study of 271 patients that compared serological tests with histological tests, 10% of biopsy samples were unacceptable for interpretation, mainly owing to poor orientation[59]. The variability in the pathological interpretation of biopsies can result in not only the underdiagnosis of coeliac disease but also the overdiagnosis of the condition[60,61], a subject that has received little attention.

An interpretation by the pathologist requires not only the correct orientation of the biopsy samples but also an adequate sampling of the duodenum by the endoscopist. It is recommended that four or more biopsy samples be taken from the descending duodenum[62], mainly because of the patchy nature of villous atrophy[11] and the variability in the orientation of the individual samples. However, a review of >100,000 duodenal biopsy reports from a large US pathology service revealed that >4 biopsy samples were taken from only 35% of patients and that the majority of the patients had only one or two biopsy samples taken. In addition, there was a linear relationship between the number of biopsy samples and reports of villous atrophy[11]. This finding again illustrates the importance of adherence to guidelines. Studies have indicated that biopsies of the duodenal bulb are necessary to confirm the pathological diagnosis of coeliac disease in some patients[5,31]. However, because of the quality of bulb specimens, caution should be taken in the interpretation of duodenal bulb biopsies in children[63].

The 2012 ESPGHAN guidelines included a score for the diagnosis of coeliac disease, and such composite scoring systems should be tested as a useful and novel way of thinking about coeliac disease diagnoses. The ESPGHAN working group advocated taking a second blood sample because of the possibility that anti-TG2 levels might be transiently elevated, in particular in young children, and that assay variability can be decreased, avoiding a false-positive test result. To increase accuracy, EMA testing is recommended as it has the highest specificity[18]. Lastly, histocompatibility antigen determination was included because either HLA-DQ2 (DQA1*0501, DQA1*0505) or HLA-DQ8 (DQB1*0201, *0202) is positive in >99.6%

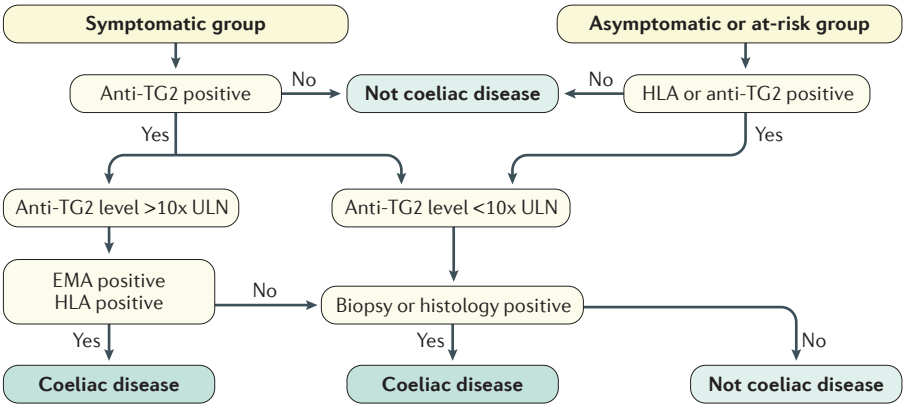


Figure 1 | **Suggested biopsy-avoiding diagnostic pathway for coeliac disease.** Non-biopsy diagnosis of coeliac disease based on the European Society for the Study of Paediatric Gastroenterology, Hepatology and Nutrition criteria in a symptomatic child with strongly positive tissue transglutaminase 2 antibody (anti-TG2) values, >10 times the upper limit of normal (ULN), a positive endomysial IgA antibody (EMA) on another blood sample and the presence of the appropriate HLA type. On the right is the process for an asymptomatic or at-risk child. A positive anti-TG2 result should lead to biopsies and histological analysis for diagnosis.

of patients with coeliac disease[64]. However, this HLA positivity also occurs in 30–40% of the general population, leading to a high sensitivity but low specificity[65] for ruling out coeliac disease if the results are negative.

Further studies have questioned the additional usefulness of HLA determination in routine testing[66]. The HLA haplotype can be closely related to the anti-TG2 response. The cut-off of ten times the ULN of anti-TG2 was chosen based on the work of Hill *et al.*[33] as described earlier, and a number of studies have since supported this view[39,67]. However, further studies of more precise cut-offs would be worthwhile to perform. The ESPGHAN guidelines recommended the use of two algorithms, one for symptomatic children and one for asymptomatic children, in line with the observation that pre-test probabilities determine serological test performance with satisfactory results in most assays from a pre-test probability of 0.10 (REF. 68). Symptoms and signs of coeliac disease or the patient belonging to a group with high risk of coeliac disease will increase the pre-test probability to at or above this level in most cases[69]. Importantly, the diagnostic process includes a follow-up of the patient to ascertain that a satisfactory clinical and serological response occurs after the adoption of a GFD.

The major advantage of the non-biopsy approach is to avoid upper endoscopy, which usually requires general anaesthesia or deep sedation in children and adolescents, along with their inherent risks[70,71]. However, the procedural risks are low in experienced hands[72]. Costs must be taken into account as well — whether imposed upon the individual patient or the health insurance or health care system — given the typically high endoscopy, pathology, anaesthesia and hospital fees incurred for a single procedure, as seen at least in the USA. After diagnosis, an observational period while the patient is on a GFD constitutes an important part of the diagnostic process, given that in children and adolescents the differential diagnoses of coeliac disease include infection with *Helicobacter pylori* or other pathogens, as well as eosinophilic oesophagitis, the latter being weakly associated with coeliac disease[73]. In contrast with adults, missing more worrisome diagnoses is unlikely in children. Cancer, including rare enteropathy-associated T cell lymphoma[74], is not a differential diagnosis in practice, as gastrointestinal cancers are extremely rare in childhood and adolescence[75].

If the patient is asymptomatic and is tested because of a concurrent disease such as autoimmune conditions (type 1 diabetes mellitus or autoimmune thyroid disease)[76,77], chromosomal aberrations (for example, Down syndrome or Turner syndrome)[78] or coeliac disease in a first-degree relative, the ESPGHAN 2012 guidelines recommend another approach. In these instances, the ESPGHAN 2012 guidelines recommend performing a biopsy in all cases. As the occurrence of transient anti-TG2 positivity in children with an autoimmune disease can be common[46], the guidelines recommend repeating anti-TG2 testing if the level of positivity is <3 times the ULN.

***Advantages of diagnosing childhood coeliac disease by biopsies.*** Several important considerations exist regarding when and whether to consider a coeliac disease diagnosis without a biopsy in children. Extrapolating the cut-off levels proposed in the ESPGHAN[6] or BSPGHAN[53] guidelines to populations outside of Europe and the UK could be problematic. Proposed anti-TG2 cut-off levels were examined in a network of European laboratories for which test norms were well-described[6,53]; however, the same might not be true for other regions, including the USA. Furthermore, anti-TG2 assays have been validated in mainly white populations and might not suit populations in other geographical areas[79]. Anti-TG2 levels are typically measured by enzyme-linked immunosorbent assay, with inherent possibilities for quality control measures. For coeliac disease diagnosis to rely on serology, laboratories should preferentially participate in control measures on a regular basis, such as the National External Quality Assessment Service initiative in Europe, even though the use of this quality-control instrument should not be over-rated[42]. No such body exists in the USA. A risk factor for the misdiagnosis of coeliac disease is the use of non-standardized tests, perhaps even those performed in suboptimal surroundings that do not meet the preconditions of the published guidelines mentioned previously. This issue is a particular threat for point-of-care tests, which are of documented value for screening[21] but are not quantitative and do not qualify as final diagnostic tests. Studies of the variety of anti-TG2 assays used in the UK pointed to pitfalls in attempting to generalize cut-off values and suggested the local validation of test kits[44,67]. When the latest ESPGHAN guidelines were implemented in a small study of North American children, 98.2% were diagnosed with coeliac disease; however, the remaining 1.8% (four patients) in the study were biopsy-negative and would have erroneously been prescribed a GFD at that point[80], although it is not clear whether this is attributable to test performance or population selection.

Missed diagnoses of upper gastrointestinal pathologies are a concern for the no-biopsy protocol. In a retrospective analysis, additional unanticipated diagnoses were found in 10% of symptomatic children who would have been eligible for a no-biopsy coeliac disease diagnostic procedure[81]. An increased association has been described between eosinophilic oesophagitis and coeliac disease[82,83], and although eosinophilic oesophagitis can cause symptoms that overlap with coeliac disease, it will not respond to a GFD. There might also be a benefit to having a baseline sample of a patient's mucosal lesion obtained during biopsy, which can be useful for comparison in cases in which improvement might not be as rapid or complete as expected. If an upper endoscopy and biopsies have not been undertaken, persistent symptoms would prompt the performance of an endoscopy in a child who did not have an initial biopsy. Potential psychological ramifications, such as anxiety and ambivalence to adhering to the GFD, of lacking a biopsy-proven diagnosis are also worthy of consideration, particularly for older children and adolescents. Future studies are warranted to determine whether forgoing a biopsy might interfere with long-term dietary adherence.

Finally, we consider that the major concern for the no-biopsy diagnostic approach is that it might not be implemented fully or correctly. Coeliac disease awareness among physicians in, for example, the USA is low, with only 17% of those with coeliac disease diagnosed, according to a study published in 2015 of data collected by the National Health and Nutrition Examination Survey[84]. There are many steps in the ESPGHAN algorithm that need to be followed and that might not be adhered to for a symptomatic child: referral to a paediatric gastroenterologist; anti-TG2 level >10 times the ULN; repeat blood tests at another time; and genetic testing. In our experience, asymptomatic children with type 1 diabetes mellitus and children with a relative with coeliac disease have been advised to start a GFD after one positive anti-TG2 test. Similarly, a symptomatic child with one positive anti-TG2 test might be advised to start a GFD. Clearly, both of these clinical scenarios do not comply with the biopsy-avoiding algorithm. If the complete standards of the guidelines are not met, a diagnosis of coeliac disease is uncertain, with an increased number of both false-positive (overdiagnosis) and false-negative cases (underdiagnosis). Although a no-biopsy diagnosis might be appropriate for children with coeliac disease who fulfil stringent criteria, advocating for such a protocol in regions where there is less awareness of coeliac disease than of a GFD might open a door to overdiagnosis and undertreatment for those not referred to experienced providers. It is recognized that the guidelines could appear complicated and will probably be revised in the future.

## Conclusions

The diagnosis of coeliac disease has traditionally rested on the finding of abnormal duodenal biopsies showing characteristic changes. The new biopsy-avoiding approach in the ESPGHAN guidelines followed the demonstration that high titres of anti-TG2 levels enable a diagnosis of coeliac disease in a well-described group of children without the use of endoscopy and biopsies. This approach has not been advocated for adults, for whom biopsies for diagnosis are always recommended. If a no-biopsy policy is to be adopted for children, the diagnostic steps outlined in the published ESPGHAN guidelines need to be closely followed to prevent both the overdiagnosis and underdiagnosis of coeliac disease. A proper diagnosis is particularly important when children reach adolescence and transition their care into adulthood, a time when both the patient and the new medical caregiver might question the veracity of the original coeliac disease diagnosis[85]. However, if the diagnosis in childhood has been made according to the strict ESPGHAN guidelines, there should be no question about the validity of the diagnosis. Nevertheless, concerns about these new guidelines have prevented their universal application. These concerns include the potential for a missed coincident pathology that would be detected at endoscopy, although this pathology would be picked up in subsequent encounters with the patient. In addition, there is concern regarding whether the appropriate cut-off values of the different anti-TG2 kits are applicable in different populations and, most importantly, whether the algorithm is followed strictly. The potential for both the underdiagnosis and the overdiagnosis of coeliac disease is great, and both of these situations have far-reaching consequences.

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