Necessary Additional Points

Studies have confirmed an increased prevalence for developing microscopic colitis in patients with sprue, and vice versa (1–3). For collagenous colitis, the reported prevalence of sprue is 3.46% (1). In patients with confirmed sprue who continue to have symptoms in spite of adherence to their restriction diet, collagenous colitis and lymphocytic colitis should always be excluded.

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Conflict of interest statement
Prof Tomm has been reimbursed for conference delegate fees, travel costs, and hotel expenses. He has also received honoraria from the Falk Foundation for preparing continuing medical educational events.

Two-step approach

The authors reference as the basis for their summary the different evidence based guidelines that have been developed over recent years, and a literature search, whose search strategy included, among others, all publications from the past 10 years identified by using the search terms "celiac disease" and "diagnosis" (1). Unfortunately they did not include our article that was published in 2013, even though this article was based on long years of experience and aimed to reach a definitive diagnosis using a minimum number of biopsies (2).

The best diagnostic test is that which results in the fewest false-positive and false-negative diagnoses; for this reason we'd suggest the following approach:

- The first step: simultaneous measuring of IgA and IgG antibodies specific for deamidated gliadin peptides, IgA antibodies specific for human tissue transglutaminase (in addition, total IgA). Most patients will either have a positive reaction to all three tested antigens or will test negative to all three of the specific antibody tests. In both these groups, biopsy is therefore unnecessary, since the positive predictive value (ppv) is 99% and the positive likelihood ratio (lr+) 87, whereas the negative predictive value (npv) is 98% and the negative likelihood ratio (lr-) 0.01. The results become even more meaningful (ppv 99%, lr+ 86; npv 100%, lr- 0.00) (2) if a fourth test is done for IgA endomysial–specific antibodies (2).
- The second step is small bowel biopsy. It is necessary only in patients with contradictory antibody results—that is, in patients who were positive in one or two tests only. This "two-step approach" reduces the proportion of patients requiring a biopsy to one-fifth (3, 4).

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The authors declare that no conflict of interest exists.

In Reply

S Razeghi focuses on the importance of symptoms in the ESPEGHAN recommendation for the rare case in which a duodenal biopsy is not needed (in a child or adolescent with at least tenfold raised anti-TG2-IgA and EMA confirmation, positivity for HLA-DQ2 or DQ8). If this is applied in any symptom that raises suspicions of celiac disease (for example, abdominal pain), the expected result will be diagnostic overkill. The ESPAGHAN guidelines refer, among others, to the Dahlborn study (reference 27 in our article) (1), in which a highly significant or a significant difference in the TG2-IgA titers existed between children with severe malabsorption and mild symptoms. Vivas et al (2) also showed that children with celiac disease do not only have higher TG2-IgA than adults, but are also more likely to have "classic" symptoms (malabsorption, diarrhea, failure to thrive). The law on genetic testing was correctly cited, but gastroenterologists can also acquire a qualification for "specialty related human genetic counseling" and therefore be allowed to screen asymptomatic patients at risk of celiac disease using the HLA-DQ2/8 genetic test.

The suggestion by A Bürgin-Wolff and F Hadziselimovic—to determine anti-TG-IgA as well as IgA and IgG antibodies against deamidated gliadin peptides, was not supported in the article by Giersiepen et al. (reference e5 in our article), after evidence-based evaluation of 2510 studies of the diagnostic potential of celiac serology testing. Current (prospective) studies are investigating this diagnostic approach. With all due respect for non-invasive diagnostic tests, and in the absence of a diagnostic gold standard for celiac disease, thorough histology of representative duodenal biopsy specimens according to March cannot be omitted, especially as the complication rate of diagnostic gastroduodenoscopy is near 0%.

We thank K Abendroth for pointing out that malabsorption of vitamin D and calcium in active celiac disease results in osteomalacia, not osteoporosis. This may be the case where a sole mineralization disorder is suspected. In celiac disease and other inflammatory bowel disorders, however, bone formation is impaired in general, among other reasons due to increased breakdown of collagen type I. This is partly explained by the release and activity of proinflammatory cytokines, such as interleukin-1α and TNFα in the context of intestinal inflammation (3). Accordingly, an increased fracture rate has been observed in

long-term untreated celiac disease in children, but especially in adults. This risk of fracture does not, as a rule, disappear after mere calcium and vitamin D substitution (4).

K Tromm mentions an important differential diagnosis for celiac disease, especially in adults: microscopic colitis, which is present as a comorbidity in 3–4% of celiac patients. In 6% of patients with "refractory celiac disease," microscopic colitis was identified as the cause (5). We did not include this differential diagnosis in the table because it does not affect the small bowel. We concede, however, that it needs to be considered in patients whose celiac disease is in remission but who continue to suffer from diarrhea.

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Conflict of interest statement

Prof. Schuppan holds a patent for an anti-TG2 test and receives license fees for its use. He has received reimbursement of conference participation fees and of travel and accommodation expenses, and has been paid for the preparation of continuing medical education events, by the Schär, Merckle Recor-dati, and Instrumentation Laboratory companies.

Prof. Zimmer states that he has no conflict of interest.