# 2020 Update of the Guidelines for diagnosing Coeliac disease published by the European Society of Paediatric Gastroenterology, Hepatology and Nutrition

In 2012 the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) has issued diagnostic guidelines for coeliac disease (CD) that should support physicians in accurately diagnosing CD without performing duodenal biopsies in selected patients. These guidelines have now been updated, new clinical evidence for this approach has been implemented and the non-biopsy approach has been evaluated also in asymptomatic children.

**European Society Paediatric Gastroenterology, Hepatology and Nutrition Guidelines for Diagnosing Coeliac Disease 2020**

Steffen Husby, Sibylle Koletzko, and their team of co-authors from various European centers, came to the conclusion that

"**CD diagnosis can be accurately established with or without duodenal biopsies if given recommendations are followed.**

- For initial testing, the combination of total IgA and IgA class antibodies against transglutaminase 2 is more accurate than other test combinations.
- The no-biopsy approach for coeliac disease diagnosis is safe in children with high serum IgA class antibody concentration against transglutaminase 2 values (≥ 10 times the upper limit of normal, ULN) with appropriate tests and positive endomysial antibodies (EMA-IgA) in a second serum sample.
- Children with positive IgA class antibodies against transglutaminase 2 but lower titers (<10 times ULN) should undergo biopsies to decrease the risk of false positive diagnosis.
- Human leukocyte antigen testing and presence of symptoms are not obligatory criteria for a serology-based diagnosis without biopsies."

Comparative to many other autoimmune diseases, antibody testing in CD does not always show a clear black and white picture. As the authors point out, children with low levels of Anti-Tissue Transglutaminase (TTG) IgA antibodies (< 10 times ULN) should undergo endoscopic biopsy, with several biopsies taken from the distal duodenum and from the duodenal bulb.

**"Discordant results between TTG-IgA and histopathology may require re-evaluation of biopsies. Patients with no or mild histological changes (Marsh 0/I) but confirmed autoimmunity (TTG-IgA/EMA-IgA+) should be followed closely."**

The studies of the working group clearly demonstrate that anti-TTG ELISAs are reliable laboratory tools that contribute significantly to disease management in coeliac disease patients.

**Methodology approach**

Taking into consideration the 2012 ESPGHAN and the 2016 published NICE Guidance Coeliac disease: recognition, assessment and management (https://www.nice.org.uk/guidance/ng20), the working group addressed 10 clinical questions to derive diagnostic recommendations. For each topic, a literature search was conducted; and the combined study results were analyzed and evaluated to develop the recommendations.

**Questions & Answers**

1. **Who should be tested?**

Testing is recommended in children and adolescents with the following gastrointestinal or extra intestinal symptoms or specific health conditions.

**Symptoms indicative for CD:**

Chronic or intermittent diarrhea
Chronic constipation not responding to usual treatment
Chronic abdominal pain
Distended abdomen
Recurrent nausea, recurrent vomiting
Weight loss, failure-to-thrive
Stunted growth/ short stature
Delayed puberty, amenorrhea
Irritability, chronic fatigue
Neuropathy
Arthritis/arthralgia
Chronic iron-deficiency anaemia
Decreased bone mineralization (osteopenia/osteoporosis), repetitive fractures
Recurrent aphthous stomatitis,
Dermatitis herpetiformis–type rash
Dental enamel defects
Abnormal liver biochemistry

**Conditions related to an elevated risk of CD:**

First-degree relatives with CD
Autoimmune conditions: type-1-diabetes, thyroid disease, liver disease
Down syndrome, Turner syndrome, Williams-Beuren syndrome
IgA deficiency

2. **Does determination of HLADQ2 or DQ8 genes contribute to the diagnosis?**

If a patient tests negative for HLA DQ2 and DQ8, the risk of CD is very low, whereas a positive result does not confirm the diagnosis, thus HLADQ2 and DQ8 genotyping is not recommended.

3. **How does the algorithm proposed to avoid biopsies in symptomatic patients work in asymptomatic subjects?**

CD can be diagnosed without duodenal biopsies in asymptomatic children, using the same criteria as in patients with symptoms.

4. **Which serological test is the most appropriate to diagnose CD?**

in subjects with normal serum IgA values for age, TGA-IgA should be used as the initial serological test regardless of age.

5. **Should more than 1 serological test be used and, if so, what should be the sequence of testing?**

Testing for total IgA and TGA-IgA as initial screening in children with suspected CD is recommended. In patients with low total IgA concentrations, an IgG-based test (DGP, EMA or TGA) should be performed as a second step.

6. **A diagnosis of CD may be safely done (positive predictive value >95%) with omission of biopsy, at which cutoff for TGA-IgA ( ≥ ULN x 10, x 7, x 5 )?**

For CD diagnosis without biopsies, TGA-IgA serum concentration of at least 10 times ULN should be obligatory. Omitting biopsies in IgA deficient cases with positive IgG-based serological tests is not recommended!

7. **Is endomysial antibody test (EMA) testing necessary in every case to diagnose CD with omission of biopsy?**

In children with TGA ≥ 10x ULN, and parents/patient agreement to the no-biopsy approach, the CD diagnosis should be confirmed by a positive EMA-IgA test in a second blood sample.

8. **What is the inter- and intra-observer variability regarding CD diagnosis of histopathology results of duodenal and bulb biopsies? What degree of lesion is considered to be untreated CD? Do duodenal bulb biopsies increase the detection rate of CD?**

At least 4 biopsies from the distal duodenum and at least 1 from the duodenal bulb should be taken for histology assessment during a gluten-containing diet. Reading of biopsies should be performed on optimally orientated biopsies. A villous to crypt ratio of <2 indicates mucosal lesions. In cases of discordant results between TGA-results and histopathology, re-cutting of biopsies and/or second opinion from an experienced pathologist should be requested.

9. **Does Marsh 0 or 1 (increased IEL counts only) compared with Marsh 0 have a different long-term outcome regarding diagnosis of CD in children with coeliac autoimmunity (positive TGA or EMA)?**

Check the gluten content of the diet and the correct orientation of biopsies before diagnosing potential CD to. Once confirmed, potential CD requires clinical and laboratory surveillance (serology, further biopsies) to monitor possible evolution to villous atrophy. For follow-up, it is important to refer the patient to tertiary care centres with expertise in CD.

10. **How often are other clinically relevant diagnoses missed if upper endoscopy is not performed in patients diagnosed by the no-biopsy approach?**

The decision to omit upper endoscopy with biopsies can be taken without the consideration of missing other pathologies or diagnoses.

**Algorithms**

In the 2020 update paper, the complex algorithms from the 2012 ESPGHAN guidelines have been modified and combined to a common algorithm for diagnosis of coeliac disease in patients with normal IgA, and patients with low or absent IgA, with or without duodenal biopsies. See figure one for a compact presentation of the algorithm for diagnosis of CD.

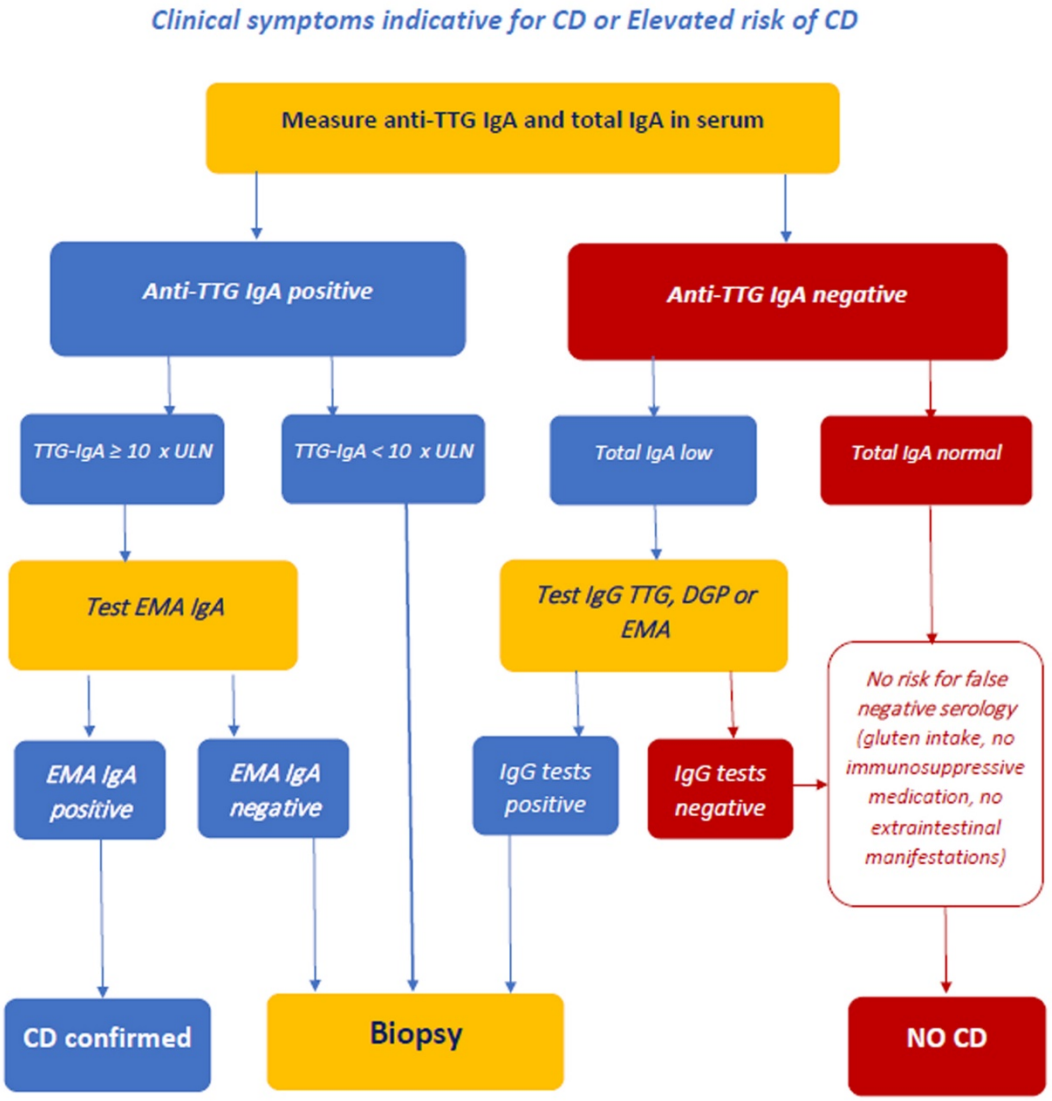


*Figure 1: Algorithm for diagnosis of coeliac disease*

**Practical aspects of anti-TTG testing**

Evaluating anti-TTG IgA test results in the low range, near the test cut off, is always a challenge. These samples demand high diagnostic competence of the lab physician and the pediatric gastrointestinal specialist. Taking into account possible risk factors for false negative results (e.g. the patient has already started a gluten free diet before testing, in patients with dermatitis herpetiformis serology is often negative, IgA deficiency), they should decide on further procedures, eventually consider endoscpic biopsy, if necessary, check the test value in relation to the cut off and repeat the test if the result is questionable or borderline. However, according to the authors' opinion, there is no need to retest if the measurement has been performed using a validated assay with a calibration curve. Also, for difficult patient samples, these Anti-TTG assays are reliable diagnostic tools, and form an essential part of coeliac disease patient management.

**ORGENTEC kits for coeliac disease serology**

ELISA:
Anti-Tissue-Transglutaminase IgA - ORG 540A
Anti-Tissue-Transglutaminase IgG - ORG 540G
Anti-Tissue-Transglutaminase IgG - ORG 540S

Anti-DGP IgA – ORG 551A
Anti-DGP IgG – ORG 551G
Anti-DGP IgG – ORG 551S

Alegria:

Anti-Tissue-Transglutaminase IgA - ORG 240A
Anti-Tissue-Transglutaminase IgG - ORG 240G
Anti-Tissue-Transglutaminase IgG - ORG 240S

Anti-DGP IgA – ORG 251A
Anti-DGP IgG – ORG 251G
Anti-DGP IgG – ORG 251S