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# New Horizons in Celiac Disease

**Celiac disease (CD) is a systemic, immune-mediated disease triggered by gluten in genetically susceptible individuals and characterized by gluten-dependent clinical symptoms, disease-specific antibodies, the presence of HLA DQ2 or DQ8, and intestinal damage (1). In patients with type 1 diabetes mellitus, a stronger association between the two conditions has been observed.**

Celiac disease is one of the gluten-related disorders, distinct from non-celiac gluten sensitivity and from IgEor non-IgE-mediated wheat allergy.

It presents with a range of **GI and extraintestinal symptoms** ***(Table 1)***, some of which are shared across the three conditions. However, symptoms such as steatorrhea, delayed puberty, poor growth, anemia, and dermatitis herpetiformis are more characteristic of CD.

Of note, CD has specific serology not present in the other two, and although villous atrophy is not pathognomonic of CD, the other two conditions occur without villous atrophy.

In recent years, thanks to studies such as the Spanish Registry of Celiac Patients younger than 15 years (REPAC 2 Study) and others (2), it has been observed that due to improvements in diagnosis, **classical forms of CD have decreased, with a rise in extraintestinal and/or subclinical forms and asymptomatic cases** ***(Table 2)***, with a **higher age at diagnosis** (6–9 years) compared with the data from the previous national registry REPAC 1 (3).

**Clinical presentation and spectrum of gluten-related symptoms in celiac disease**. The changing presentation of CD and future directions for improving diagnosis: (A) The "classic" presentation of diarrhea, weight loss, and malabsorption still occurs in very young children, but is much less likely in older children and adults. (B) Currenltly, most patients present with symptoms resembling irritable bowel syndrome (IBS), anemia, osteoporosis, and other extraintestinal signs, or they are asymptomatic and detected by screening. (C) CD remains widely underdiagnosed, and to address this problem, improved case finding strategies combined with universal or targeted screening and accurate, non-invasive diagnostic approaches are needed.

**Prevalence** studies of CD range between 0.26–3.03%, **averaging about 1% of the population** (4). Recent studies show that incidence has been increasing in recent years, by about 7.5% per year, more frequently in women and children (5).

A large proportion of the population remains undiagnosed—so-called **"hidden prevalence"**—mainly due to asymptomatic forms of the disease, with long-term consequences. »

**TABLE 1**

**Consider the diagnosis of celiac disease (CD) in the presence of the following symptoms, signs, or circumstances**

| | |
|---|---|
| **GI symptoms:** | • Chronic or intermittent diarrhea / Chronic constipation / Chronic abdominal pain<br>• Abdominal distension<br>• Recurrent nausea or vomiting |
| **Extraintestinal symptoms:** | • Failure to thrive / Weight loss / Growth stagnation / Short statur<br>• Chronic iron-deficiency anemia<br>• Delayed puberty, amenorrhea<br>• Recurrent oral aphthae<br>• Chronic fatigue, irritability<br>• Fragile bone fractures / Osteopenia / Osteoporosis<br>• Neuropathy<br>• Arthritis, arthralgia<br>• Dermatitis herpetiformis<br>• Dental enamel defects<br>• Abnormal liver function tests |
| **In children and adolescents belonging to the following risk groups:** | • First-degree relatives of individuals with CD<br>• Autoimmune diseases: Type 1 diabetes, Autoimmune thyroid disease, Autoimmune liver disease<br>• Down syndrome<br>• Turner syndrome<br>• Williams-Beuren syndrome<br>• IgA deficiency |

**TABLE 1.** Symptoms, signs, or circumstances to consider in the diagnosis of CD. ESPGHAN (European Society for Paediatric Gastroenterology, Hepatology, and Nutrition), adapted from the original source, 2020.

**TABLE 2**

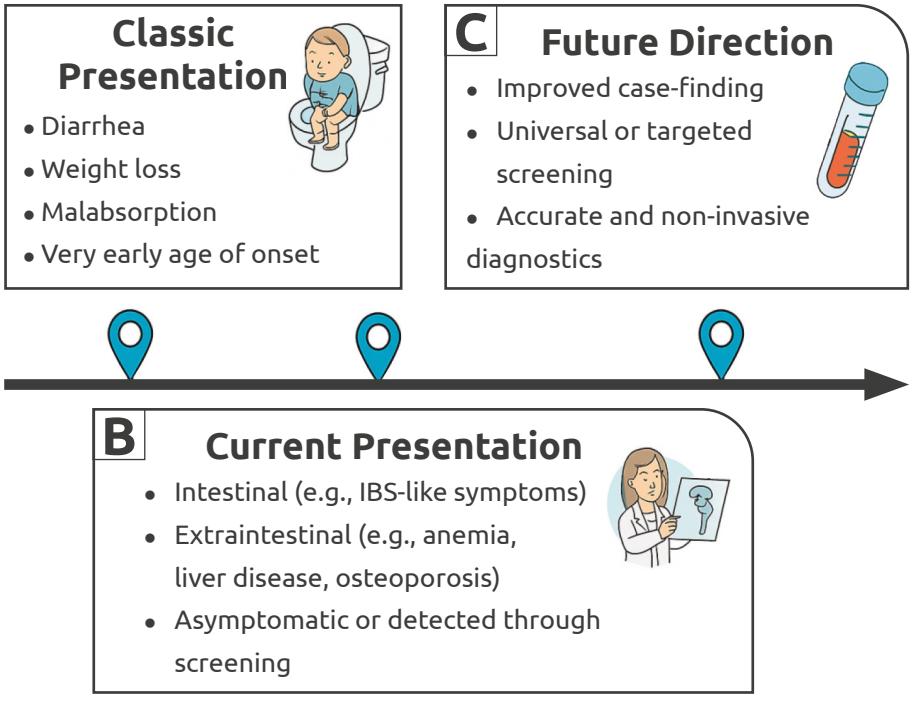


**TABLE 2:** Adapted from Adams DW. Gastroenterology 2024 (2).

## IT IS A HIGHLY PREVALENT DISEASE IN BOTH CHILDREN AND ADULTS, WITH A WIDE VARIETY OF SYMPTOMS, WHICH SOMETIMES MAKES EARLY DIAGNOSIS DIFFICULT

» This has raised one of the most relevant debates today: whether to implement **universal screening** for CD to increase early diagnosis.

Italy has been the first country in the world to initiate population-wide screening. Since January 2024, Italy has, by law, established universal screening for CD in children aged 1–17, as well as screening for type 1 diabetes. It is the first country with such legislation for both conditions.

This decision was motivated by a study led by Carlo Catassi's group at the Universidad Politécnica de Marche, published in early 2023. This was a multicenter study evaluating CD prevalence and diagnosis rates in Italy across different regions and school-aged children, using universal screening with HLA DQ2-DQ8 testing (excluding children already diagnosed with CD). Children with compatible HLA underwent blood tests for anti-tissue transglutaminase IgA (tTG-IgA) or deamidated gliadin peptide IgG antibodies (IgG anti-DGP) in IgA-deficient children. Anti-endomysial antibody (EMA) was tested in a second serum sample in cases with positive results, and per ESPGHAN guidelines, intestinal biopsy was performed when EMA was positive and tTG-IgA levels were >1x and <10x the upper normal limit, or IgG anti-DGP was positive with IgA deficiency (6).

Diagnosis of CD was establisjed in cases with:

1. **Positive tTG-IgA,** positive EMA, and villous atrophy (Marsh-Oberhuber grade 3) in small intestine biopsy.

2. **tTG-IgA levels** >10x ULN and EMA positivity in two separate samples.

3. **Positive IgG anti-DGP,** IgA deficiency, »

» and villous atrophy (Marsh-Oberhuber grade 3).

The study reported a prevalence of 1.65%, one of the highest worldwide.

They concluded that without screening, 60% of children would have remained undiagnosed: of every 100 children, 60 were diagnosed through the study and 40 were already known. This result motivated the legal decision to implement screening.

Of those diagnosed, 43.7% had no symptoms, while 56.3% had suggestive symptoms that had gone undetected. This finding confirmed that symptom-based case-finding (i.e., testing only symptomatic individuals) is not efficient enough, **whereas population-based screening is the most effective way to identify asymptomatic patients and prevent morbidity from delayed diagnosis.** »

| Nº | WHO Criterion |
|---|---|
| 1 | The disease must constitute an important public health problem. |
| 2 | There must be an accepted treatment for detected cases. |
| 3 | Adequate facilities for diagnosis and treatment must be available. |
| 4 | The disease should have a recognizable latent or early stage. |
| 5 | A suitable, valid, safe, and acceptable screening test must exist. |
| 6 | The test must be acceptable to the target population. |
| 7 | The cost of screening must be justified in relation to total health care spending. |

**TABLE 3:** WHO criteria, population disease screening

**ITALY, ONE OF THE COUNTRIES WITH THE HIGHEST PREVALENCE OF CD, HAS, SINCE JANUARY 2024, APPROVED BY LAW, UNIVERSAL SCREENING FOR CD IN CHILDREN AGED 1–17 YEARS, AS WELL AS SCREENING FOR TYPE 1 DIABETES**

» In addition, 14.6% had first-degree relatives with CD but had never been tested before.

Then, why is universal screening for CD not widely implemented?

There is ongoing debate as to whether CD meets the criteria for population-based screening.

According to the WHO, for screening to be recommended, a disease must fulfill seven criteria ***(Table 3)***:

It should be common and well defined, with quick, safe, precise, and culturally acceptable tests, available treatment, and difficult clinical detection. The debate in CD focuses on the last two points: whether CD causes serious and preventable complications if treated, and whether tests and treatment are cost-effective.

A 2017 JAMA review concluded there was insufficient evidence to support universal CD screening, mainly because of insufficient evidence that screening **asymptomatic people** effectively prevents serious long-term complications like osteoporosis or lymphoma (8). No subsequent studies have refuted this conclusion.

**Asymptomatic patients are harder to detect clinically,** less likely to have high antibody levels or severe biopsy lesions and tend to have milder disease and lower risk of severe complications. They may also have poorer adherence to a gluten-free diet due to the absence of symptoms.

Nonetheless, an **important argument in favor of screening is that early diagnosis** and treatment could prevent serious long-term complications, especially since some patients will remain asymptomatic.

The key question is whether **screening can truly diagnose, treat, and reduce complications earlier than clinical suspicion in routine practice would allow**.

Another example comes from the Netherlands, where, under a different health care organization, preventive medicine centers are widely attended by the population. Through the "Glutenscreen" initiative, all children aged 1–4 undergo a rapid tTG test, even if asymptomatic, along with a health »

## AN IMPORTANT JUSTIFICATION FOR SCREENING IS THE SIGNIFICANCE OF EARLY DIAGNOSIS AND INITIATING TREATMENT AS SOON AS POSSIBLE TO PREVENT THE DEVELOPMENT OF SERIOUS FUTURE COMPLICATIONS

» questionnaire listing possible CD-related symptoms and family history (9).

Between 2019–2022, more than 5,000 children were studied. A total of 43% exhibited symptoms for which they had never sought care. Rapid tests were performed, with 1.9% testing positive, later confirmed serologically in 1.7%. The number of diagnoses was double the initial estimate. These results have motivated incorporation of rapid testing into routine preventive care, following a targeted questionnaire, as a cost-effective, efficient, ethically sound, and well-accepted strategy.

An alternative proposal is "opportunistic screening," which involves testing for CD serology whenever a child is having blood drawn for another reason (10). However, more data are needed on this approach.

As we can see, the available data point toward increasing the early diagnosis of CD to prevent long-term complications arising from underdiagnosis, which is particularly important in asymptomatic patients—thereby justifying screening according to the relevant studies. D

### CONCLUSIONS

Italy has opened the door for other countries to consider universal CD screening.

This strategy proposes detecting CD across the whole population, beyond traditional risk groups, although clinical suspicion continues to play a key role.

Classic forms (diarrhea, malabsorption, etc.) are now less common, while subclinical, extraintestinal, and asymptomatic forms predominate, complicating early diagnosis.

The future, based on current data, should move toward active case-finding, screening, and more sensitive, specific, and non-invasive diagnostic approaches.

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