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**TITLE PAGE**

**Title:** Screening Individuals with Irritable Bowel Syndrome-type Symptoms for Celiac

Disease: Time for a Rethink?

**Short “running” title:** Screening for Celiac Disease in IBS.

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**Abbreviations:**

IBS	irritable bowel syndrome
GI	gastrointestinal
tTG	tissue transglutaminase

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Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal (GI) disorder, characterized by abdominal pain or discomfort and altered bowel habit.<sup>1</sup> Many patients with IBS also report troublesome bloating, or visible abdominal distension. The condition affects between 5% and 20% of the population,<sup>2</sup> depending on the criteria used to define its presence, and is commoner in women and younger individuals.<sup>2,3</sup> Although IBS is not a diagnosis of exclusion,<sup>4</sup> with physicians advised to minimize invasive investigations, the symptoms of IBS are not specific,<sup>5</sup> and may occur in several other organic GI conditions.<sup>6-8</sup>

Celiac disease is a chronic immune-mediated enteropathy, characterised by T cell sensitisation to gluten in genetically predisposed individuals. The prevalence of a positive serological test for celiac disease in the US and European community is estimated to be between 0.8% and 1.0%.<sup>9,10</sup> Patients with celiac disease can present with GI symptoms such as abdominal pain, bloating, and diarrhea. These symptoms may be overlooked, leading to mislabeling as IBS, and a delay until the diagnosis of celiac disease is established.<sup>11</sup> It is important to distinguish between IBS and celiac disease, as the treatments are quite different. Patients with celiac disease are advised to adhere to a lifelong gluten-free diet, whereas patients with IBS are usually treated symptomatically, often using pharmacological or psychological therapies aimed at providing relief of the predominant symptom reported.<sup>4,12</sup>

Some studies have demonstrated that patients who report symptoms compatible with IBS are more likely to have positive celiac serology, and biopsy-proven celiac disease, than controls without such symptoms.<sup>6,13</sup> A previous meta-analysis of observational studies demonstrated a pooled prevalence of biopsy-proven celiac disease in suspected IBS of 4.1% (95% confidence interval 1.9% to 7.0%), and a four-fold increase in the odds of biopsy-proven celiac disease compared with people without IBS-type symptoms.<sup>14</sup> An economic analysis, conducted from a US perspective, suggested that testing patients with suspected IBS became cost-effective when the prevalence of celiac disease exceeded 8%,<sup>15</sup> close to the

upper limit of the estimated prevalence of biopsy-proven celiac disease in individuals meeting criteria for IBS in the meta-analysis. Partly as a result of these findings, current guidelines for the management of celiac disease advise physicians to screen patients consulting with IBS-type symptoms routinely via serological testing.<sup>16, 17</sup>

In this issue of *Clinical Gastroenterology and Hepatology* Choung et al., report data from Olmsted County, MN that, at first, appear to question the utility of this approach.<sup>18</sup> The authors conducted a cross-sectional questionnaire survey of 7217 residents in the community, collecting data on symptoms compatible with functional GI disorders, including IBS. These symptom data were linked to prevalence surveys of undiagnosed celiac disease conducted among >47,000 individuals within the same region, using immunoglobulin A tissue transglutaminase (tTG), followed by confirmatory endomysial antibody testing in those with a positive tTG.

There were 3196 subjects whose data were available from both studies, of whom 434 (13.6%) had IBS according to the questionnaire used. In total, 31 (1%) individuals were seropositive for celiac disease, but only one (3%) of these met criteria for IBS, compared with 433 (14%) of those with negative celiac serology. This suggests the yield of testing people reporting symptoms compatible with IBS is low. However, of note is that subjects were no more likely to report other GI symptoms felt to be typical presenting features of celiac disease than those without. These included abdominal pain (19% in those testing seropositive vs. 25% in those who were seronegative), diarrhea (3% vs. 9%), bloating (5% vs. 23%), or abdominal distension (0% vs. 14%), and seropositive individuals were also less likely to report any GI symptom (45% vs. 55%).

The strength of this study, conducted among the general population in the US, is also one of its inherent weaknesses. Prevalence studies of this type, which examine the epidemiology of functional GI symptoms, work on the premise that the prevalence of true

organic disease in individuals reporting GI symptoms in the community is low, so it is perhaps no great surprise that only one of the people with IBS-type symptoms tested seropositive. In addition, current guidelines do not recommend screening people with symptoms compatible with IBS in the general population for celiac disease, regardless of whether they have consulted a physician. The studies that these guidelines based their recommendations on were, for the most part, conducted among patients consulting with GI symptoms.

An issue that remains unclear is the temporal relationship between symptoms and the dates serological samples were obtained. It is well known that GI symptoms in the community fluctuate,<sup>19</sup> yet the point at which people were reporting symptoms compatible with IBS and the time at which they returned a positive serological test is unclear. In addition, individuals with celiac disease diagnosed around the time the serum samples were drawn were excluded from the analysis. It would be useful to know how many individuals' data were excluded on this basis as, if these subjects were reporting symptoms compatible with IBS at the point the diagnosis of celiac disease was secured, the results of the study could change. Finally, the mean age of included individuals at the time of the survey was 61 years. Celiac disease has a bimodal age distribution and, in the US, IBS is commoner in younger individuals.<sup>20</sup>

A previous large study conducted in a US referral population demonstrated a similarly low prevalence of biopsy proven celiac disease of 0.4% in 492 patients with non-constipated IBS, questioning the value of opportunistic screening even in patients consulting with suspected IBS in the US. The well-designed and rigorous study conducted by Choung et al. demonstrates a low yield of testing individuals reporting symptoms compatible with IBS in the community for celiac disease, leading them to conclude, justifiably, that testing in this setting is unlikely to have a significantly increased yield over population-based screening.

However, it should not lead to a change in recommendations for practice in either primary or secondary care in other countries.

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