Our responses to the comments of Reviewers and the Editors

We thank the editors and the reviewers for their time and consideration of our paper. The manuscript is stronger after incorporating these recommendations. Please find the point by point response to the questions below. Our replies are in blue.

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: Celiac disease is a chronic gluten-induced enteropathy with plethoric manifestations. In this review article, the authors summarized the available literature about the prevalence of celiac disease in various gastrointestinal (chronic diarrhea) and non-gastrointestinal conditions. share the various clinical indications for screening for Celiac disease. Also, elucidate the diagnostic performance of various serological assays along with their limitations and propose a diagnostic algorithm for patients with suspected celiac disease.

Authors: Thank you.

However, there were some problems in this article.
1.Probable indications for screening for CeD. Suggest adding Indicators of laboratory and instrument testing.

Authors: Thank you for this point, we have added a flow diagram summarizing the indications for the various tests based on the current guidelines.

Manuscript: We have suggested a testing schematic for the various indications for suspected CeD in **Figure 2**.

2. Suggest searching multiple databases to avoid missing literature. It is suggested to add the latest relevant literature.

Authors: Thank you for this point, we have also searched Embase and Scopus databases for the studies on the various diseases that are included in the study. The manuscript has been suitably modified and the references are updated.

3. That patient with symptomatic diseases described in this article should be tested for celiac disease. Therefore, the clinical implication of this article is not significant. It is recommended to summarize a set of diagnostic schemes.

Authors: Thank you for this point. The prior studies including the WGO guidelines published in 2016 have covered many of the clinical conditions associated with Celiac disease. However, our study also summarizes the present literature on these studies and provides in-depth analysis for the readers. By discussing the present evidence, we discuss our rationale for the recommendations. We also highlight the present knowledge gaps and the unmet needs for future studies in these areas.

4. It is recommended that disease of the same system be grouped together.

Authors: Thank you for this point, we have re-arranged all the diseases in the review based on the organ systems under the heading of definite, probable, and possible indications for the screening for disease. Also, we have added figure 1 where all the conditions are reported system-wise.

5. It is suggested to express the research results in the form of charts. Or other forms, more intuitive.

Authors: Thank you for this point, we have added the Figure 1 in the study to graphically represent all the included results.

Reviewer #2:

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: In this manuscript entitled "Who and How to Screen for Celiac Disease": the authors categorized different atypical symptoms associate with celiac disease as definite indications, probable indications, and possible conditions. And the diagnostic performance and limitations of these serological tests were discussed. Additionally, the diagnostic ideas for patients with suspected celiac disease are proposed.

Thank you.

However, there were some problems in this study.

1. The 2016 WHO global guidelines have indicated that patients with symptomatic diseases described in this article should be tested for celiac disease. Therefore, the clinical implication of this article is not significant.

Authors: Thank you for this point. The WHO guidelines do cover most of the clinical conditions covered in our paper however, it does not report the exact prevalence of Celiac disease in the

various conditions and the quality of the present literature. Our study summarizes the present literature on these studies and provides in-depth analysis for the readers. By discussing the present evidence, we discuss our rationale for the recommendations. We also highlight the present knowledge gaps and the unmet needs for future studies in these areas.

2. Suggest adding the elaboration on the pathogenesis of celiac disease and further elaborate on the relationship between typical and atypical symptoms of celiac disease in the introduction.

Authors: Thank you, we have added the pathogenesis of Celiac disease in the introduction and have briefly alluded to the atypical symptoms in celiac disease.

Manuscript: "The disease is related to a complex interaction between genetic, environmental and immunity-related factors. It is triggered by ingestion of gluten, a protein present in cereals such as wheat, barley, and rye in genetically-predisposed individuals. The phenotypic expression of CeD is variable. It ranges from being completely asymptomatic to severely symptomatic disease.(2,3) Also, CeD once thought to affect only small intestines, is now considered a multi-system disorder. While there are convincing clinical and epidemiological evidence of involvement of extra-small intestinal organs, the exact pathogenesis of their involvement remains unexplored. It is likely that the HLA-DQ2 restricted gliadin peptide induced T-cells which originate in the small intestine, circulate in peripheral blood and home in other organs leading to organ specific cell injury.(4,5)"

3. Suggest adding the specific division basis of Definite indications for screening for CeD, Probable indications for screening for CeD and Probable indications for screening for CeD.

Authors: Conditions that reported a prevalence of Celiac disease >4% were considered "definite" indications for the screening for Celiac disease while conditions reporting a prevalence of 2-4% of Celiac disease were considered "probable" and those with less than 2% of prevalence with celiac disease was considered "possible" indications for screening for Celiac disease.

4. Suggest searching multiple databases to avoid missing literature

Authors: Thank you for this suggestion, we have also searched Embase and Scopus databases for the studies on the various diseases that are included in the study. The manuscript has been suitably modified and the references are updated.

5. In the part of patients with iron deficiency anemia, suggest adding the reason for the sudden mention of vitamin B12 deficiency in iron deficiency anemia and further discuss the causes of different prevalence rates caused by geographical factors.

Authors: Thank you for this point, we have removed B12 deficiency in the section to improve the flow of the section. Also, we agree different prevalence rates are affected by the geographical factors and have expanded on these points in the manuscript.

6. It is recommended that disease of the same system be grouped together, such as liver disease, cryptogenic cirrhosis, and auto-immune hepatitis.

Authors: Thank you, we have re-arranged all the diseases in the review based on the organ systems under the heading of definite, probable, and possible indications for the screening for disease.

7. Suggest tabulating the studies involved in the manuscript to make the summary clearer.

Authors: Thank you, we have updated the Table 1 with the references to all the studies and to report the prevalence of Celiac disease in the various reported conditions.

Our responses to the comments of Reviewer for second-round review

We thank the editors and the reviewers for their time and consideration of our paper. The manuscript is stronger after incorporating these recommendations. Please find the point by point response to the questions below. Our replies are in blue.

Reviewer #1:

Thanks for inviting me to re-review the manuscript. All of the suggestions have been responded point to point, and the manuscript is better elaborated with detailed revisions. It offers clinical lessons about who and how to screen for celiac disease. It is such a good idea to illustrate the screening indications and diagnostic flow by figure, but I do suggest that Figure 2 could be polished to be more concise. I suggest minor revision.

Author reply: Thank you so much for your encouragement and prompt review of the manuscript. We have tried to further improve the Figure 2 to make the flow diagram more concise.