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Recommendations to Quantify Villous Atrophy in Video Capsule Endoscopy Images of Celiac Disease Patients

We thank the reviewers and editor for their kind assistance in improving the quality of the manuscript. We have implemented all suggestions.

Reviewer #1

Dear Authors, I have read with interest your nice paper, which I consider useful for your Journal. I only suggest, to ameliorate the paper, to add, in the introduction, a brief overview of other endoscopic tools, beyond videocapsule endoscopy, for the diagnosis of celiac disease, including chromoendoscopy, Fujinon Intelligent Chromo Endoscopy, Narrow Band Imaging, Optical Coherence Tomography, Water-Immersion Technique (both in adults and children), confocal laser endomicroscopy, high-resolution magnification endoscopy, and I-Scan technology, with pertinent (original) references Good Job! best wishes

We thank the reviewer for this kind sentiment. We have now included thee in a new subsection in the Discussion, 'Other Methods' which discusses these other technologies.

Reviewer #2

This paper is very confusing and non-interesting for a reader because it has too many technical details. Information regarding the interaction with clinical data is lacking. Although this is an interesting topic the authors were unable to make it interesting for the reader.

We apologize for this problem. In the revised manuscript we have taken care to eliminate confusing portions and to rewrite as needed for clarity.

Reviewer #3

In their paper, Ciaccio et al. suggest that villous atrophy can be detected and mapped in a sequential series of videocapsule images by computerized means. If areas of villous atrophy could be detected and mapped automatically all along the small intestinal tract, it would potentially be very helpful in the diagnosis of celiac disease (CD) and to monitor CD patients. In this work they aimed to describe the main modes of quantitative detection of villous atrophy from videocapsule endoscopic images, and possible avenues to improve the detection rate and to

better monitor the severity and types of pathology present in endoscopic images which are abnormal due to the presence of villous atrophy. they suggest that the introduced bias based on observer experience would be obviated by computerized techniques.

Comments This is a very intriguing and important issue. However, this article shows technical aspect that are important to those with closely related research interests. I am not qualified concerning the computerized techniques described, so I am basing my review on the assumption that these methodologies are appropriate and properly conducted. However, also the Authors pointed out that nowadays there are geographic regions with lesser reported frequencies of celiac disease that may simply be regions with a lack of experience in diagnosis and/or area lacking the facilities necessary for definitive diagnosis[2].

In my opinion this paper raises several issues that should be taken into account. First of all cost-effectiveness studies should examine whether VCE is a cost-saving approach in the evaluation of CD patients. It is difficult to believe that area lacking the facilities necessary for definitive diagnosis would have the possibility to use this device. Secondly its role in this setting is rather limited because of the inability to perform small-bowel biopsies that are necessary to confirm the diagnosis. However, unnecessary biopsy procedures could be avoided in the future by these new approaches, only in the event that positive findings from large, randomized trials including cost analyses and clinical outcome evaluations will be performed. Only then a change in practice for the diagnosis of CD will be possibly approved by a panel of experts and accepted by the health authorities. The discussion should be more focusing on the limitations of the study and on the need of further studies that are mandatory to understand the role of video capsule endoscopy in CD.

We thank the reviewer and do now incorporate into the revised manuscript a new subsection of the Discussion to show potential advantages of the videocapsule system i.e., 'Particulars of the Videocapsule Technique'. This new text includes information on cost-effectiveness, and comparison with conventional endoscopy.

#### Reviewer #4

In this paper authors describe methods to quantify the presence of villous atrophy in endoscopic images. The goal of video capsule endoscopy is to improve the detection rate and to better monitor the severity and types of pathology present in endoscopic images. Capsule endoscopy has many practical limitations of use in celiac patients. Video capsule endoscopy is useful to determine the length of the small intestinal mucosa affected, and visualization of lower parts of small bowel mucosa. In celiac patients we have to determine the selected subpopulation in which the capsule endoscopy may be beneficial. The diagnosis of CD and follow-up is supported by the clinical signs, prevalence of symptoms, presence of CD-related autoantibodies and may include further biopsies. Future studies must show where is the real need for video capsule endoscopy.

We thank the reviewer and in the revised manuscript we now include a new subsection of the Discussion to show potential advantages of the videocapsule system i.e., 'Particulars of the Videocapsule Technique'.