April 8, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 9304-review.doc).

Title: Molecular Markers and Imaging Tools to Identify Malignant Potential in Barrett's Esophagus

Authors: Michael C. Bennett and Hiroshi Mashimo

Name of Journal: *World Journal of Gastrointestinal Pathophysiology*

ESPS Manuscript Number: 9304

We thank the reviewers for their time and consideration in evaluating our manuscript. We have made the following improvements in accordance with their suggestions:

1. We have revised the language and formatting to improve clarity and ease of reading and to meet WJGP specifications.

2. With respect to the scope of the article, we sought to review current literature on biomarkers in a broad sense, not limited to biochemical markers. We wished to raise the point that even if individual markers were to prove efficacy in the range of 30-60% sensitivity and specificity, the significant issue of sampling error would remain. Using standard Seattle protocols, less than $1/40^{th}$ of the mucosal surface is sampled, with immunohistochemical stains typically performed on only a few sections representing less than $1/100^{th}$ of that specimen. Limited sampling is a major concern in light of the small and seemingly randomly dispersed foci of dysplasias in the setting of Barrett's esophagus. A logical "next step" to impact morbidity and mortality from esophageal adenocarcinoma is to use a broad imaging modality or improved sampling technique to be coupled with traditional biomarkers for the detection of early dysplastic lesions. In response to the reviewer's comments, we have made substantial revisions to the organization of the manuscript and discussion intended to clarify and strengthen this point.

3. We thank the reviewer for comments regarding the importance of serum biomarkers for the future of expanded screening. We have incorporated the references on p53 as a promising marker into a new section on serum biomarkers

and have moved discussion of a promising biomarker panel from serum samples into this section as well.

4. We thank the reviewer for suggestions regarding incorporation of recent literature regarding RTKs. We have expanded discussion of these and added references. We have also touched on the very promising work in therapeutics using antibodies to RTKs such as EGFR and HER2; a more in-depth discussion of these advances is outside the scope of our article, which focuses on diagnostic and predictive modalities.

5. References have been updated and formatted according to WJGP specifications.

Thank you again for considering our manuscript for publication in the *World Journal of Gastrointestinal Pathophysiology*.

Sincerely yours,

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