

Format for ANSWERING REVIEWERS



September XXX, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 4866-revised.doc).

Title: Colonic manifestations of *PTEN* hamartoma tumor syndrome: case series and systematic review

Author: Peter P Stanich, Robert Pilarski, Jonathan Rock, Wendy L Frankel, Samer El-Dika and Marty M Meyer

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 4866

The manuscript has been improved according to the suggestions of reviewers and editors as follows:

1. Revision has been made according to the suggestions of the reviewer as follows. The reviewer notes are copied, with our responses included in bold and the updated text included in italics below them.

Reviewer 1: In this paper, the authors analysed and reviewed patient data from their institute and literature to identify the connection between gastrointestinal abnormalities (in particular colon lesions/cancer) and *PTEN* hamartoma tumor syndrome (PHTS) to make recommendation for future clinical examination of patients. The study was well organized and clearly set up. The authors reported that PHTS had a high prevalence of colonic polyposis. It will be interesting to know the connection of the high prevalence of colonic polyposis in PHTS patients to the risk of gastrointestinal (colon in particular) cancers.

We appreciate the thoughtful review and kind words and agree this is an area that needs further investigation.

What is the cost effect if patients are given colonoscopy at age 35 or 10 years younger than the earliest colorectal cancer diagnosis in a first-degree relative with future surveillance intervals based on the results?

We agree this is a very interesting question, although our data and any available data with regards to the colon manifestations of *PTEN* hamartoma tumor syndrome are inadequate to answer this query. As we mention in our discussion, there is no data available on the outcomes from colon cancer, colon polyps and efficacy of surveillance programs in this population. Accurate baseline data in these fields are necessary to run the models needed to determine cost effectiveness. However, surveillance programs for Lynch syndrome have been shown to be cost-effective and reduce mortality so until more information is available, we feel surveillance is indicated based on current data. We have thus expanded our discussion to include the need for future research to define the optimal surveillance program and included further investigation into this area in our COMMENTS section in the "Research frontiers" portion.

"Further investigation is needed in this area to clarify the optimal surveillance protocol and to allow for adequate counseling and treatment of PHTS patients with GI polyposis."

*"Research frontiers: Continued investigation into the malignant potential and clinical outcomes of colonic polyposis in the *PTEN* hamartoma tumor syndrome, including cost effectiveness of colon cancer surveillance."*

Other concerns: the percentages calculated in the Results (first paragraph) for the Abstract need to be checked.

We have clarified the abstract to alleviate this concern. Our initial wording did not make it plain that the percentages were calculated with respect to patients that had received colonoscopy and not the entire initial cohort of all patients that had undergone any endoscopy, leading to the concerns of the reviewer. We have simplified the opening as well as eliminated the reported percentages in question.

"RESULTS: Eight patients from our institution met initial inclusion criteria. Of these, 5 patients underwent 4.2 colonoscopies at mean age 45.8 ± 10.8 years. All were found to have colon polyps during their clinical course and polyp histology included adenoma, hyperplastic, ganglioneuroma and juvenile. No malignant lesions were identified. Two had multiple histologic types. One patient underwent colectomy due to innumerable polyps and concern for future malignant potential. Systematic..."

Reviewer 2: This is a very interesting report summarizing the literature and underlining the literature by findings of their own cases. although a rare disease, this study reads very interesting for clinicians. Great und congratulations.

We appreciate the thoughtful review and kind words.

2. Format has been updated, including changing to the 10 pt font as directed, standardizing the inclusion of author degrees on the title page and clarification of author contributions.
3. To fit with BPGs revision policies for Brief Articles, we have made several small changes. We have amended to the title to fit within the word limit, additional relevant key words were added, and minimally edited the Table headings.
4. A spelling error was noted and the letter "p" has been added to the word phosphatase on page 2 and page 5.
5. Based on Editor comments, we expanded the Methods and Results section of the abstract to meet the word requirement.
6. The "Core Tip" on page 3-4, the Methods on Page 6 and the Results on Page 7 were edited slightly for clarification and to improve readability.
7. COMMENTS section was completed per Editor request. The Peer Review portion was left blank as we were unsure of how much of the reviews should be inserted in this area.

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

Sincerely,

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