

October 23rd, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: ESPS 5156-review.doc).

Title: Patient perceptions of stool DNA testing for pan-digestive cancer screening: a survey questionnaire

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- The manuscript has been improved according to the suggestions of reviewers. We appreciate their constructive comments and have included the appropriate changes in our revised manuscript or response as detailed below:

Reviewer 00061684

- 1) COMMENT #1: "This is an interesting manuscript. While the questionnaire showed acceptance among the persons asked it will then be shown in practice how many are really undergoing the testing"

Response: We appreciate the reviewer's input. Whether the overall positive response to MUST will translate to utilization once it is available remains to be determined; however, these preliminary findings encourage further development and testing of MUST. Perceptions of MUST were favorable, and perceptual barriers were not identified.

Reviewer 00831111:

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- 1) Comment #1: "MUST is still an early study. Its sensitivity and specificity should be mentioned in the introduction. More details about pan GI screening of MUST should also be discussed in the introduction".

Response: We have expanded the Introduction section to include details regarding previous studies on stool-DNA testing for supra-colonic GI malignancies. Specifically, we summarize detection rates of supracolonc digestive cancers observed in early studies.

- 2) Comment #2: "The patient interest is affected by the perfectness of MUST. This limitation should be addressed".

Response: We address this directly in the Discussion section by acknowledging that MUST is a hypothetical rather than actual product and whether patients' interest in MUST translates to actual utilization when available remains to be determined. Further, we have added the following : "Our survey can only assess perceptions, attitudes, and likelihood of using a hypothetical MUST in comparison to already available CRC screening modalities. As such,

respondents' perceptions of MUST may have been affected by its conceptual appeal and the lack of information on actual performance on cancer screening".

- 3) COMMENT #3: "This study focused on pan-digestive screening. What is the rationale to include airway cancers?"

Response: Lung, breast and prostate are among the most common cancers in the United States. We included these cancers in the survey to assess respondents' general knowledge of cancer and their concern of developing any of these cancers in addition to other gastrointestinal malignancies. Furthermore, there is early evidence that central lung cancers may be detectable by stool DNA testing, as tumor-derived DNA is present in sputum that is regularly swallowed and excreted with stools.

- 4) COMMENT #4 and #5: "Two references are missing. P value for stool DNA test is missing in figure 1".

Response: We have made the appropriate revisions in the text and figure.

Reviewer 00070310

- 1) COMMENT #1: "The authors mentioned that stool DNA testing was useful for detecting pan-digestive cancer. Please show the data except colorectal cancer".

Response: As above, we have expanded the Introduction section to include details regarding previous studies on stool-DNA testing for supra-colonic GI malignancies.

- 2) COMMENT #2: "Please show MUST in detail and impact the effect of MUST".
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Response: MUST is a hypothetical test that is currently not available. However, we discuss in the Introduction section previous studies on stool-DNA testing for supra-colonic GI malignancies and expand with details on the advances in this technology for colorectal cancer screening.

Reviewer 02446451

- 1) COMMENT #1: "I am surprised and concerned that the study has not gone through the ethical committee in their institution".

Response: As stated in the Methods section, the study was reviewed and approved by the Internal Review Board at Mayo Clinic. The study aimed at evaluating patients' perceptions of stool-DNA testing for pan-digestive screening through a survey questionnaire. The study was considered a minimal-risk investigation by the IRB.

- 2) COMMENTS #2: "I am uncertain why the authors choose their study group from the Mayo Clinic registry. Quite clearly this is going to be a bias response from this selected group. I do not think this sample is representative of the views from the general population. At least we cannot extrapolate the data that way and this I think is the main criticism of this paper. Furthermore with this selected group of patients, the response rate is only 36%. I think the conclusion is only valid for Mayo Clinic registry and cannot extrapolate further. The paper could be enhanced by including this study in the general population not in heavily biased selected group of patients from Mayo clinic".

Response: We fully agree that a general population will need to be appraised to corroborate our findings, and state this in the Discussion. This was an exploratory study designed to evaluate patients' perceptions of stool-DNA testing for pan-digestive screening. The Mayo Clinic registry was used in order to identify participants with accessible demographic information to facilitate contact via mail for the survey questionnaire. We agree that our study group lacks the demographic diversity of the general population and acknowledge this as a potential limitation in our discussion section. However, the positive perception of a stool-DNA test for cancer screening in this study is congruent with previous findings. In a multi-center study, Schroy and colleagues [9] reported patients' preference for stool-DNA testing over fecal occult blood and colonoscopy for routine CRC screening. Interestingly, the authors report that this preference for stool-DNA testing did not vary significantly on the basis of age, gender, race/ethnicity, and family history. Hence, the positive response to MUST in our study group may still translate into acceptance from a more diverse population. Further studies are needed to corroborate these initial findings.

We also recognize that response bias could have influenced our results and address this by comparing early respondents (returned the survey in ≤ 3 months) and late respondents (returned survey > 3 months). Patient demographics were similar between these two groups and interest in using MUST remained high, without any statistically significant differences observed (Supplemental Table 2). In spite of this analysis, we still acknowledge potential for response bias as a potential limitation in our discussion section.

- 3) COMMENT#3: "It would be good to include the questionnaire in this paper. It allows the readers to scrutinize the broad questions that were asked and whether they were phrased in such a way that would generate bias responses from the study group. There is also no attempt by the authors to pilot the questionnaire prior to sending out to the patient group. No reliability analysis (Cronbach alpha) were carried out on the 29-item survey questionnaire".

Response: We have included the survey questionnaire as a supplement to the manuscript. Our survey questionnaire was designed in collaboration with the Mayo Clinic Research Center. The questions were modeled and standardized after those developed in the Health Information National Trends Survey (HINTS) 2007 on perceived risk, screening behavior, knowledge and concern about cancer. This was designed as an exploratory survey to evaluate perceptions and preferences for MUST and thus the survey tool was not piloted or reliability analysis performed. We have edited the original manuscript to include this point as a potential limitation in the interpretation of the results. This has been highlighted in our discussion section.

- References and typesetting were corrected
- Format has been updated

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

Sincerely yours,



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