September 13, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format: **12431-Review.docx**

Title: Current state of early detection of pancreatic cancer and an approach for future: expanding the higher-risk group with clinical and metabolomics parameters

Author: Shiro Urayama

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 12431-edited

The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

(1) Reviewer 00043116:

Comment #1: "*Page 2, line 8-9. Authors wrote as following: 'In this article, we will review the current status of the PDAC cancer detection/diagnostic modalities'*"
Response: Since the emphasis of this article is on the early PDAC detection, we have focused on the EUS as the commonly utilized imaging technology for identification of the smallest pancreatic lesions – we have modified and clarified this point in the manuscript.

Comment #2: "*Page 2, line 16. Refs [19-22] were published almost 20 years ago. It would be better to update and cite more recent papers.*"
Response: we have updated the references.

Comment #3: "*Can authors summarize current early detection schemes of pancreatic cancer in figure or table?*"
Response: Based on the current recommendation from International CAPS Consortium, we have included a paragraph describing this – however, due to many of the undefined nature of the recommendation, we opted not to make it into a concrete figure or table.

Comment #4: "*Page 10, line 12-16. Authors wrote as following: 'As we continue to translate the advancement of biological understanding of PDAC, we strongly anticipate useful biomarkers would become available in the near future which would help to identify the significantly higher-risk individuals within the general population for developing early-stage PDAC' But in this paragraph, I'm not sure what is the advancement of biological understanding of PDAC, and what advancement can be a useful biomarker. Please write more clearly referring previously published papers. Or it might be better to delete this sentence.*"
Response: The sentence was deleted in the revision.

Comment #5: "'*Translational Research-Application of Metabolomics Approach' section. Overall, this section is not so specific to PDAC. Authors explained how important metabolomics in cancer progression generally. It is not clearly reviewed what metabolomics of PDAC can affect progression of PDAC, and can be a biomarker. For example, how are associations of p53, Akt1, or HIF with PDAC? Can these markers be an effective biomarker for PDAC? Because this is a review for PDAC, they need to focus on PDAC more specifically.*"
Response: We have revised the paragraphs for the applicability of metabolomics approach and relevance to PDAC biomarker analyses.

Comment #6: *"'Translational Research-Application of Metabolomics Approach' section. Please explain the importance of the Warburg effect in PDAC with some references."*
Response: The revision includes the edited paragraph with the Warburg effect in PDAC with references.

Comment #7: *"Authors wrote as following: 'As such, metabolomics biomarker application for breast, prostate, esophagus, liver, kidney, ovarian, colorectal cancers have been reported by various groups'. Are there any papers about metabolomics biomarkers applications for PDAC?"*
Response: Multiple references of PDAC metabolomics biomarker applications are listed. We have rephrased the paragraph, so that the PDAC applicability is clarified.

Comment #8: *"Page 12, line 8-13. Why can amino acids, bile acids, and a number of lipids and fatty acids be a biomarker for PDAC? Please briefly explain."*
Response: Some clarification on this matter is included in the paragraph.

Comment #9: *"Figure 1. Is it authors' research data? Review paper usually doesn't include authors' research results. Or just an example?"*
Response: The figure is a demonstration (an example) of discriminant metabolites set which allows distinction of the cancer cases from the benign conditions. The Figure Legend was updated to emphasize this fact.

Comment #10: *"Figure 1. Can authors add explanation about which small molecules or metabolites have a potential to discriminate PDAC from control based on this figure 1?"*
Response: The purpose of the figure is to demonstrate the discriminant capacity of a set of metabolites, further supporting the rationale for this approach in PDAC; we have elected not to delve into the specific molecules for this paper. This information would be included in another paper with associated potential implications and further investigation with biological ties, in order not to lengthen the current manuscript.

(2) Reviewer 00054993:
Comment: *"Ref. 30 and 31 lack their years of publication"*
Response: The missing reference data were supplied.

(3) Reviewer 00503452:
Comment: *"The article is well written even if the paper is too long and some concepts are repeated in the text in different paragraphs (see familial pancreatic cancer)"*
Response: The paragraphs were revised to reduce redundancy.

3 References and typesetting were corrected

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

Sincerely yours,

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