Dear editor in chief,

Thank-you for considering our review entitled '**Pancreatic cancer: a review of clinical diagnosis, epidemiology, treatment and outcomes'** for publication in the World Journal of Gastroenterology. We appreciate the reviewer's comments and have made the necessary changes. Please see our response to these below.

Reviewer 03548113. No changes recommended

Reviewer 00009064

Table 1. Please replace various by variable.

Response: This has been changed in Table 1.

Figure 2: In the section on Limited evidence/ please group the factors according to positive or negative evidence irrespective of how weak the evidence is. It does not make sense to lump fruits and vegetables with high glycaemic control and fat as the reader is left wondering which one of them is likely to be good and which one harmful.

Response: The current phrasing in the results text for this evidence is "Other dietary factors with limited suggestive evidence in pancreatic cancer aetiology include foods and beverages containing fructose, or foods containing saturated fatty acids; while no conclusions could be made with regards to other dietary exposures." The related Figure, which is reproduced from the World Cancer Research Fund (as referenced), visually shows that these factors are considered as having limited evidence for increasing the risk of pancreatic cancer; this is also inferred through our use of 'pancreatic cancer aetiology' in the accompanying text. We do not feel it is appropriate to assign a positive or negative/ good or harmful judgement to the remaining dietary factors in the 'limited – no conclusion' category, since the World Cancer Research Fund judged the evidence for this as inconclusive either way.

Table 3: Please indicate in each histological variant the difference in outcome as compared with the garden variety adenocarcinoma. At present you have indicated that only in colloid/mucinous carcinoma.

Response: The outcomes of each of the morphological variants compared with adenocarcinoma has now been updated within Table 3.

Reviewer 03538158

How about androgen receptor expression in the pancreatic cancer? Authors should mention about this.

Response: We agree that this is useful information for the review and the role of androgen receptor expression in pancreatic cancer is now discussed within the *Molecular understanding of pancreatic adenocarcinoma pathogenesis* section on page 24 lines 24-31.

Authors should mention about intraductal mucinous papillary neoplasms (IPMN) in the risk factor of pancreatic cancer section.

Response: In our review, we have considered IPMN as a pre-malignant condition, and its role in pancreatic cancer development is described in detail in the pathogenesis section (page 23). As a pre-malignant condition it is thereby inferred that this is a risk factor through which pancreatic cancer may arise.

In Diagnosis and screening section, Magnetic Resonance Imaging/Magnetic Resonance Cholangiopancreatography (MRI-MRCP) should be described more.

Response: The role of MRI/MRCP has now been described in more detail within the *diagnosis and screening* section on page 25 line 14-26.

Authors referred the paper published by Bailey P [69], who classified pancreatic cancer into 4 types by various recent molecular techniques. Authors should mention them in detail.

Response: This classification has now been described in more detail in the *Molecular understanding of pancreatic adenocarcinoma pathogenesis* section page 24 line 16-21.

Reviewer 02445708

Liquid biopsy in pancreatic cancer as diagnostic and therapeutic tools should be discussed.
Response: We have discussed the lack of evidence that exists regarding the use of blood biomarkers within the *Biomarkers for Early Detection* section on pages 26-27 and the necessity for further research. We have now included the term liquid biopsy (page 26 line 16) within this section to demonstrate to the readers that this is interchangeable with the terminology used for blood biomarkers.

Administration of virotherapy, synthetic vectors, and gene-editing technology to treat pancreatic cancer should be discussed.

Response: A Paragraph titled *Future directions* has been added on page 34 lines 4-10 and includes some information on these topics. This was comprehensively reviewed by Rouanet et al in 2017 and there has been little new evidence published in this field since then. The reader is therefore directed to this review but detailed analysis is not provided given the lack of new evidence since this publication.

The influence of gut microbiota on pancreatic cancer should be discussed.

Response: This is a very good suggestion in a highly topical area. A new section entitled *Gut microbiota* has been added on page 9 lines 15-21 and outlines the key findings from a systematic review published on the role of gut microbiota in pancreatic cancer in 2017.

We hope that our review is now considered as suitable for publication in the *World Journal of Gastroenterology*, and can consider any further suggestions if necessary.

Many thanks

Stephen McCain