

Dear Editor and Reviewers:

I appreciate your comments on the manuscript. Per your advice, we have amended the relevant parts of the manuscript. Some of your questions are answered below.

**Response to reviewer #1:**

1. If the cost of the test is not taken into account, it seems to be a very efficient test method, but there is no comparison with the commonly performed fecal occult blood test. The authors should investigate comparative study in this cohort between Syndecan-2 DNA methylation test and fecal occult blood test with ROC analysis.

**The authors' answer:** First of all, thank you very much for your comments. We have investigate comparative study in this cohort between Syndecan-2 DNA methylation test and fecal occult blood test with ROC analysis. The results were exhibited in Fig. 2 (page 15), which demenstrated that mSDC2 testing exhibited significantly improved diagnostic sensitivity, specificity and AUC values for CRC, AA and ACN.

2.It would also add to the scientific value of this paper to clarify whether Syndecan-2 DNA methylation is found in cancerous areas or polyp tissue, or whether it is also found in normal colorectal tissue surrounding the cancer.

**The authors' answer:** Thank you for raising this point. Through the literature research, we found that that the methylation level of SDC2 in tumor tissues surpasses that in corresponding non-cancerous tissues and exceeds levels observed in polyps. As SDC2 methylation can be detected in both adenomas as well as early carcinogenesis, its methylation is considered to be a gradual process. Relative to normal colorectal tissues and polyps, SDC2 was found to be significantly more methylated in different stages of CRC pathogenesis and advanced intestinal adenoma formation. The illustration of this point was shown in line 135-146 (page 5).

## **Response to Science editor:**

### Comments to the Author

The author clearly stated the purpose of the study and the research structure is complete. However, the manuscript is still required a further revision according to the detailed comments listed below.

1)Table(s) and figure(s): There are 2 Figures and 5 Tables should be improved. Detailed suggestions for each are listed in the specific comments section.

**The authors' answer:** First of all, thank you very much for your comments. We agree with this suggestion and have revised this point in the manuscript.

2) The English-language grammatical presentation needs to be improved to a certain extent. There are many errors in grammar and format, throughout the entire manuscript. Before final acceptance, the authors must provide the English Language Certificate issued by a professional English language editing company.

**The authors' answer:** Thank you for your advice. The manuscript has been re-edited by a professional English language editing company. And the English Language Certificate has provided.

3) Please add the Core tip section. The number of words should be controlled between 50-100 words..

**The authors' answer:** Thank you for raising this point. The Core tip section has been added.

4) Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the

editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

**The authors' answer:** Thank you for raising this point. All tables has been revised in standard form.

5) The "Article Highlights" section is missing. Please add the "Article Highlights" section at the end of the main text (and directly before the References).

**The authors' answer:** Thank you for your advice, We have added The "Article Highlights" section at the end of the main text (and directly before the References).

6) Please provide all fund documents.

**The authors' answer:** All fund documents were provided in accompanying documents.

7) Please provide the primary version (PDF) of the Institutional Review Board's official approval, prepared in the official language of the authors' country.

**The authors' answer:** The Institutional Review Board's official approval was provided in accompanying documents.

8) Please provide the Clinical trial registration statement.

**The authors' answer:** First of all, thank you very much for your comment. According to "NIH Definition of Clinical Trial Case Studies ([https://grants.nih.gov/policy/clinical-trials/case-studies.htm#collapseS2\\_NIDDK\\_8](https://grants.nih.gov/policy/clinical-trials/case-studies.htm#collapseS2_NIDDK_8))". Our study was designed to validate the effectiveness of fecal DNA Syndecan-2 methylation (mSDC2) test in the detection of colorectal cancer (CRC) in high-risk population in China, as compared to the gold

standard Colonoscopy. But not to evaluate the effect of the intervention on the participants. Like Case#17 in “NIH Definition of Clinical Trial Case Studies”, we think this study is not a clinical trial. So we didn't provided the Clinical trial registration statement.

9) Please provide the filled conflict-of-interest disclosure form.

**The authors' answer:** The filled conflict-of-interest disclosure form was provided in accompanying documents.

Other revisions are labeled in yellow in the revised version of Revised Manuscript with highlighted changes.

Thanks to you and all the reviewers for your kind advice. I hope you are satisfied with the revised version. If there are additional questions, we are willing to revise the manuscript further.

Sincerely,

Wenfeng Luo