Reply to the reviewer's comments

We greatly appreciate the reviewers of the *World Journal of Gastrointestinal Surgery* for their time to review our article Manuscript NO.: 86056, Observational Study, "Comparative detection of syndecan-2 (SDC2) methylation in preoperative and postoperative stool DNA in patients with colorectal cancer." We have made a number of changes and clarifications in the manuscript based on the reviewer's comments. Revised sites were identified with red highlights.

Reviewer #1:

The authors have measured methylated SDC2 from stool samples in patients with colon cancer before and after surgical treatment. The pre-operative sensitivity was 88.6%. Sensitivity was less for early-stage disease. The post-operative test positivity rate was about 20%, higher in women. None of these false positives had recurrence. Of the 6 recurrences in 46 months of follow up, none were SDC2 positive in the post-operative sample. The data indicate that the source of SDC2 in the pre-operative sample was likely of tumor origin. The authors concluded that these observations support a use case of methylated SDC2 in post-operative surveillance. However, the impact of this application is likely low due to the high post-operative false positive rate and a lack of prediction of recurrence. It therefore seems highly unlikely that SDC2 methylation would disrupt surveillance colonoscopy for CRC survivors, who remain at risk for advanced pre-cancers, metachronous new CRC, and less often recurrence of the primary cancer.

(Answer)
Thank you for your comment. As you pointed out, we acknowledge that the conclusions of our study regarding the usefulness of postoperative surveillance were not appropriate, and we have decided to remove the statement regarding the usefulness of surveillance as a conclusion of our study.

Study strengths include: • Relatively large sample size (104 patients) • Clear study flow diagram (Fig 1) • Clear definitions of positive and negative test thresholds Addressable weaknesses include: • Lack of 95% confidence intervals around sensitivity and specificity estimates • Blank STROBE checklist (should indicate where in the manuscript the items are reported) • Missing X- and Y- axis values and legend for Fig 2 • Reporting of blinding for laboratory test operators • Lack of clear statement of involvement of Genomictree, Inc by whom 2 of the authors are employees and who markets a methylation-based CRC screening test.

(Answer)
Thank you for your comment. As you pointed out, we have calculated and included the confidence intervals for sensitivity and specificity estimates in the Discussion section, and we have filled in the STROBE checklist and added missing X- and Y- axis value and legend for Fig 2. As well as, we have described the blinding for laboratory test operators and the involvement of Genomictree, Inc by whom 2 of the authors in the manuscript.

Reviewer #2:

Authors should address implications for metastasis to rectum PMID: 28393107 and management of microbiome PMID: 35203709 If the above are addressed and references included, paper could be of interest.

(Answer)
Thank you for your valuable suggestions. We have carefully considered the implications for metastasis to the rectum (PMID: 28393107) and the management of the microbiome (PMID: 35203709). We have addressed and references included as reviewer's comments in the Discussion session.

Science editor:

The manuscript has been peer-reviewed, and it' s ready for the first decision.

(Answer)
Thank you for notifying us that the manuscript has completed the peer review process and is now ready for the first decision. We appreciate the thorough evaluation and feedback provided by the reviewers. We have carefully considered their comments and suggestions during the revision process.

Company editor-in-chief:

I recommend the manuscript to be published in the *World Journal of Gastrointestinal Surgery*. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: https://www.referencecitationanalysis.com/.

(Answer)
Thank you for recommending the manuscript for publication. We appreciate the suggestion to use the Reference Citation Analysis and have explored its benefits to supplement the latest cutting-edge research in our revision.