Dear editor-in-chief and reviewers,

We would like to thank you for providing us with an opportunity to adequately address reviewer's comments for our manuscript, entitled "Diagnostic accuracy of the multi-target stool DNA test in detecting colorectal cancer: A hospital-based study(**Manuscript NO: 79893**)" for further consideration for publication in the World Journal of Gastrointestinal Oncology.

We have taken each of the reviewers' comments into careful consideration. Below this cover letter, we address each of the comments individually.

We hope you find the revised manuscript acceptable for publication in The World Journal of Gastrointestinal Oncology, but would be pleased to have the opportunity to make further amendments, if required. Thank you once again for your consideration.

Best regards,

Yours sciencerely,

Jinqing Fan Ph.D.

Reviewer #1: The manuscript entitled "Diagnostic accuracy of the multi-target stool DNA test in detecting colorectal cancer: A hospital-based study" examined the stool DNA in CRC and may be a noninvasive biomarker for clinical diagnosis of CRC.The results are interesting and potential important. Maybe the following questions need to be considered：

1.Whether the multi-target stool DNA test increases the economic burden on the population compared to colonoscopy.

Thanks a lot for your interest in our article. While colonoscopy is highly sensitive and specific for CRC and precursor lesion detection and removal, it is invasive, expensive and resource heavy. Factors to consider include the invasiveness of the test, test performance, screening interval, accessibility, and cost. Hence, there is an unfulfilled need for multiple modality CRC screening that can improve current CRC screening rates and may be resource effective strategies. The MT-sDNA test increases patient life-years gained in CRC screening simulations[1]. Screening by MT-sDNA results in QALY savings and was cost-effective compared with screening by colonoscopy for a wide range of adherence scenarios in Alaska people[2]. While, in the United States study, they found FIT and colonoscopy to be more effective and less costly than the MT-sDNA test when participation rates were equal for all strategies. For the MT-sDNA test to be cost effective, the patient support program included in its cost would need to achieve substantially higher participation rates than those of FIT[3]. Therefore, the results are various in different countries, but there is a lack of relevant health economics research based on the Chinese population. In the following study, our team attempted to explore the cost-effective and cost-benefit of MT-sDNA test through Markov model, so as to provide a certain scientific basis for related research in China.

[1]Carethers JM. Fecal DNA Testing for Colorectal Cancer Screening. Annu Rev Med. 2020;71:59-69.

[2]Redwood DG, Dinh TA, Kisiel JB, et al. Cost-Effectiveness of Multitarget Stool DNA Testing vs Colonoscopy or Fecal Immunochemical Testing for Colorectal Cancer Screening in Alaska Native People. Mayo Clin Proc. 2021;96(5):1203-1217.

[3]Ladabaum U, Mannalithara A. Comparative Effectiveness and Cost Effectiveness of a Multitarget Stool DNA Test to Screen for Colorectal Neoplasia. Gastroenterology. 2016;151(3):427-439.e6.

2.Is this test appropriate for colorectal cancer screening in large populations or is it appropriate for screening only a subset of people, such as those with a history of adenoma.

We feel great thanks for your professional review work on our article. MT-sDNA test may not be suitable for large-scale population screening because of the high cost of testing, but it can be used as an alternative for those who are willing to pay and do not undergo colonoscopy.

3.Whether multi-target stool DNA test combination with fecal occult blood test can help improve the sensitivity and specificity.

Thank your for pointing this out. This is the research direction of our another writing article, we find that the combined test of MT-sDNA and can fecal occult blood test(FOBT) improve the sensitivity of colorectal cancer screening (preliminary results, not yet published).

4. Perhaps a multicenter study is needed.

Thank you for your good suggestion. Due to the limited project funds and the cost of genetic

testing reagents, this study was not able to carry out a large-scale, multicenter study, which is a defect of this study. If more research funding can be obtained, we will conduct multicenter studies to reduce Berkson bias in future studies.

Reviewer #2:The study of the accuracy of colorectal cancer detection tests. It should be carried out in trials with a representative sample and multicenter, as well as contemplating the diversity of the population. The study carried out presents a small casuistry, carried out in a diverse population and showed a decrease in sensitivity when compared to other studies, showing that adding carcinoembryonic antigen (CEA) to the multi target stool DNA, increased the sensitivity for detecting adenoma. Faced with the controversies of colorectal cancer markers, including doubts regarding the sensitivity of colonoscopy as a marker, recently published. Studies in this area have increased in importance. I understand that, although not fulfilling an important publication criterion, the sample size, it should be published due to the contributions regarding the sensitivity of the test.

Thank you for your interest in our research. As we know, the selection bias is inevitably of a case-control study. In future research, if there is financial support, we plan to carry out multi-center and large-sample research to reduce the bias brought by single-center research.