Peer Review File

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Review Comments:

Comment 1. Page 2: comparing the participation rate in the NordICC study to the Minnesota study should be put in the context of comparing invitation to invasive colonoscopy vs non-invasive fecal occult-blood testing.

Reply 1: We agree with the reviewer. Text edited as follows: “The reason for low participation in NordICC trial could be attributed to invasive nature of colonoscopy.”

Changes in the text Page 2 we modified as advised

Comment 2. Page 3: "it is difficult to see how the results of the NordICC trial may apply to our practice and patient populations in the U.S." The biggest takeaway from the NordICC trial that is perhaps generalizable to all settings is that inviting asymptomatic individuals to an invasive test will result in suboptimal screening uptake. Throughout the review, the authors have shown that the studies using non-invasive screening tests had a higher uptake, and this should be highlighted here as the main limitation of colonoscopy screening.

Reply 2: Per reviewer suggestion, we have modified the sentence as suggested. It now reads: While it is unknown how NordICC may apply to a US population, a generalizable finding is that asymptomatic indivduals invited to undergo an invasive test are likely to have low participation rates, leading to suboptimal screening outcomes. Page 3 edits as above. Also, Page 12 in summary points was modified as advised

Comment 3. Page 9 (Table 2): I don't think there is enough evidence to give a "53%" reduction in mortality from CRC as an advantage of colonoscopy. As we currently have conflicting data, it is better to refrain from specific statements that could be misleading to patients.

Reply 3: We have removed the statement per reviewer suggestion.

Comment 4. It would be interesting to have a short discussion about what changes the author expect to the current CRC screening pathways in the U.S.

Reply 4: We have updated the conclusion per reviewer suggestion and added the following text:
Conclusion:

Promising results have emerged from pilot studies of upcoming new tests like the blood-based mSEPT9 test and cell-free DNA, indicating their potential for future implementation. The integration of artificial intelligence (AI) and machine learning will play a crucial role for effective population-based screening.
Moreover, a growing array of image-based tests shows potential to become viable alternatives to colonoscopy in the near future. Among these modalities under development are colon capsule endoscopy (CCE), CT capsule, and magnetic resonance (MR) colonography. These advancements hold promise in revolutionizing colorectal screening approaches in the coming years.

Page 11 we modified as advised