Article details: 2016-0047	
Title	Performance of a quantitative fecal immunochemical test in a colorectal cancer screening pilot program: a prospective cohort study
Authors	Jennifer Telford MD FRCPC, Laura Gentile MHA, Lovedeep Gondara MSc, Colleen McGahan MSc, Andrew Coldman PhD
Reviewer 1	Dr. Waseem Sharieff
Institution	Radiation Oncology, Dalhousie University Faculty of Medicine, Halifax, NS
General comments (author response in bold)	1. The analysis section does not describe any analysis. How was the positive predictive value computed? **Author's Response:** A subsection on statistical analysis was added to the Methods section with the following: The positive predictive value was calculated as the number of participants with an abnormal fecal immunochemical test undergoing colonoscopy classified by the highest risk pathology finding divided by the total number of participants with an abnormal fecal immuochemical test undergoing colonoscopy. For example, the positive predictive value for colorectal cancer = number of participants with an abnormal fecal immunochemical test undergoing colonoscopy with a diagnosis of colorectal cancer/ Total number of participants with an abnormal fecal immunochemical test undergoing colonoscopy. 2. How was disease status assessed in FIT negative patients? **Author's response:** FIT negative patients did not undergo colonoscopy, which is why we used the PPV as our outcome measure. We did assess for interval CRC in FIT negative patients by linking the Colon Check participants to the BC Cancer Registry. This is reported in the Results section. 3. Could sensitivity and specificity be calculated? **Author's response:** Calculation of sensitivity and specificity was limited by the lack of colonoscopy in the FIT negative patients. Therefore, we do not know the false negative rate of FIT from colonoscopy. However, we did estimate the sensitivity and specificity of FIT for the detection of CRC using linkage to the BC Cancer Registry to determine subsequent CRC diagnoses in FIT negative patients. I had reported in the Interpretation but have removed it from the revised version after considering the reviewer's comments. 4. Could ROC analysis be done? **Author's Response:** For ROC analysis, we need False Positive Rate (FPR) and True Positive Rate (TPR). Which are calculated as the following: FPR=(False positive)/(False positive+True negative) TPR=(True positive)/(False negative+True positive) For this study we ha on the true negative and false negative False positive=FIT +ve | no disease detected True negative=FIT –ve | no disease detected True positive=FIT +ve | disease detected False negative=FIT –ve | disease detected As the participants with a negative FIT did not undergo colonoscopy, the true negative and false negative FIT are unknown. The authors may wish to refer to STARD statement. **Author's response:** The STARD checklist is attached.
Reviewer 2	Dr. Young-In John Kim
Institution	Department of Medicine, University of Toronto, Toronto, Ont.
General comments (author response in	General comments:

bold)	In this paper, Telford et al. reports performance of a quantitative fecal immunochemical test (FIT) in a colorectal screening program in British Columbia. Prospectively collected data from biennial two specimen quantitative FIT with a cut-off of 100 ng/mL buffer with follow-up colonoscopy if either test was positive in asymptomatic, average risk 50 to 74 year old men and women participating in Colon Check are presented. The detection rate of FIT for CRC was 3.5 per 1000 participants. The positive predictive value of FIT for CRC, high risk polyps and all neoplasia was 5.0% (95% CI 3.8-6.0%), 34.8% (95%CI 32.5-37.2%) and 62.0% (95%CI 59.6-64.4%), respectively. The number needed to screen to detect one CRC was 283, to detect one high risk polyp 43 was 40 and to detect any neoplasia was 22. The authors interpreted that biennial screening with a two sample quantitative FIT surpassed current benchmarks for neoplasia detection in population-based CRC screening. The study design, data analyses, statistical analyses and interpretation of the data are sound and the manuscript is clearly formulated and well written. The data from this study provide important information regarding performance of FIT as a population-based colorectal cancer screening tool. Specific comments: 1.Three BC communities participated in Colon Check. Are these communities representative of the BC general population and the Canadian general population? What were some unique characteristics of these communities? What were the primary reasons that these 3 communities were selected over other communities in BC? This is relevant regarding the generalizability of the findings to the general population. **Author's response:** The setting subsection was elaborated with the following: These communities were chosen to represent both rural and urban centers and by site willingness to participate. While not formally assessed, these communities collectively demonstrate diversity in age, gender, ethnicity and socioeconomic status, and the Colon Check results should be generalizable to the BC population as a whole. A table illustrating the characteristics of the participants in the different communities has been added to the Results section. 2. Personal history of prior colon adenomas was not an exclusion criterion. Why not? **Author's response:** Individuals with a personal history of adenomatous polyps are in a colonoscopy surveillance program typically at a 5-year interval and were excluded on the basis of having undergone lower endoscopy in the past 5 years. 3. Family history of colorectal cancer in first degree relatives was not include in the analysis. In this regard, any family history of colorectal cancer and adenomas should be included in the analysis. **Author's response:** The participants in this analysis are those that underwent FIT as the primary screening test. The participants with a first-degree relative with CRC were screened by primary screening colonoscopy and will be reported separately. The family history group in Colon Check underwent a fairly complex analysis and, the authors felt, was more appropriate as a separate publication. I have cited the abstract in the Results section. 4. Colonoscopy was performed by community colonoscopists. Who are these? Gastroenterologists, surgeons, internists, family physicians, and/or nurse practitioners? Please provide this information. In this regards, quality performance evaluation should be provided. **Author's response:** I have added the following to the Methods section: Colonoscopy was performed in the usual manner by community colonoscopists including gastroenterologists, general surgeons and an internal medicine

	specialist with additional training in colonoscopy. All colonoscopists participated in the Colon Check colonoscopy quality initiatives. 5. Of approximately 95,000 eligible subjects, 17.1% successfully completed a first round of screening with FIT. How does this number compare with other colorectal cancer screening modalities (FOB, colonoscopy, flexible sigmoidoscopy, barium enema, CT colonography)? What were some reasons for not participating in the FIT screening program? Any significant difference in baseline characteristics between those who completed and those did not participate in the FIT screening program? **Author's response:** This value is not a true participation rate for several reasons. Most importantly, as described in the manuscript, the exact underlying population to whom Colon Check was available is not known as family physician's living in a Colon Check community could refer their patients to Colon Check regardless of where that patient lived. I have removed the rough estimate of participation from the Interpretation and the rough estimate of the eligible population from the Results section and Figure 1. 6. FIT was unsatisfactory for analysis in 1.3% individuals. What does this mean? What were some reasons for unsatisfactory analysis? **Author's response:** An unsatisfactory FIT is determined by the lab and often was due to leakage of the sample. The following has been added to the Results section: The test was unsatisfactory for analysis in 1.3% of individuals, primarily due to leakage of the liquid buffer within the specimen container. 7. Although the perforation rate was comparable to that previously reported, the post-polypectomy hemorrhage rate (1.6%) appears to be higher than ~0.3 %, the general figure that are often cited. Also, the serious adverse event rate (2.9%) appears to be higher. Please explain these observations. What were some of the characteristics (patient and colonoscopist) associated with serious adverse events? **Author's response:** There was an error in reporting the serious adverse events. There were 47 unplanned events, 16 of which were classified as serious adverse events due to hospital admission. Six of these were classified as post-polypectomy hemorrhage after review by the Quality Management Committee. The other ten patients with rectal bleeding either: 1) reported self-limited rectal bleeding to the Nurse Navigator at the 14 day follow-up visit but did not require hospital admission/intervention, or 2) had bleeding during the initial colonoscopy and polypectomy with hemostasis achieved endoscopically. The following changes have been made in the Results section: Of the 1597 colonoscopies performed, 16 (1.0%) resulted in a serious adverse event probably or possibly related to the procedure. There were 3 (0.19%) colon perforations (1 immediate and 2 delayed) and 6 (0.13%) post-polypectomy hemorrhages. 8. For those who are not familiar with screening benchmarks, please provide some information re: # needed to screen with FIT to detect one CRC, one high risk polyp, and any neoplasm. How does the observed numbers compare with other screening modalities? **Author's response:** To our knowledge, no screening programs using other modalities have reported these numbers. Germany and Poland have primary screening colonoscopy programs while Australia has a population-based flexible sigmoidoscopy program. I have performed a PubMed search and was unable to locate a publication with these outcomes. There are no population-based screening programs for colonoscopy and flexible sigmoidoscopy in Canada, which would be the optimal comparison data as these results will depend on the underlying prevalence of disease in the population. Ontario has a flexible sigmoidoscopy program but it is not population based and has not published outcome data (personal communication with Dr. Jill Tinmouth,

	Lead Scientist ColonCancerCheck, Ontario). 9. Among 9 non-screen detected colorectal cancers identified in Colon Check participants, 8 had a negative FIT within 30 months preceding cancer diagnosis including 5 in stage 3 and 4. Are there any specific patient characteristics with this false negative FIT? **Author's response:** This is a very important question, particularly whether there are any characteristics about the tumor (site, morphology, histology) that affect the FIT detection. Unfortunately, due to small numbers, it is premature to draw any conclusions. Briefly, the interval cancers were distributed through age, gender and colon site. We did not have access to the tumor details such as neoplasm grade or microsatellite instability testing. 10. In this regard, what is the false negative rate of FIT and negative predictive value? **Author's response:** The false negative rate of FIT and negative predictive value could not be calculated as participants with a negative FIT did not undergo colonoscopy. Only individuals with a positive FIT had a colonoscopy. 11. The authors used the manufacturer's recommended cut-off of 100 ng/mL buffer in Colon Check. Please provide compelling justifications for choosing this cut-off value. **Author's response:** When the Colon Check began, there were no data on the performance of FIT in Canada and we elected to use the 100 ng/mL cut-off as it is the recommended cut-off by the manufacturer. The following has been added to the Methods section: This cut-off was recommended by the fecal immunochemical test manufacturer. 12. Participant compliance with follow-up colonoscopy was 88.6% due, in part, to the patient navigation incorporated into Colon Check as well as the provision of additional colonoscopy resources specifically for Colon Check participants. The authors need to discuss how feasible this approach is in the general Canadian population as well as economic impact of this approach. **Author's response:** We have not done a formal cost-analysis; however, if colonoscopy is performed to follow-up a positive FIT in a healthy screening participant, we found that assessment by a trained registered nurse prior to colonoscopy is feasible. In Colon Check, the nurse navigator assessment was done in place of a physician's consultation and associated billing. If the cost of the nurse navigator is in addition to the physician's consult fee, then the cost would need to be justified by a potentially improved rate of follow-up colonoscopy as well as the value of capturing delayed colonoscopy related adverse events. The following was added to the Interpretation: An economic analysis was not performed; however, the goal of patient navigation was to replace a physician consultation and the associated fee.