Author’s response to reviews

Title: Outcomes of screening and surveillance in people with two parents affected by colorectal cancers: experiences from the Familial Bowel Cancer Service

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Professors Jan Lubinski and Rodney Scott, Editors-in-Chief

Hereditary Cancer in Clinical Practice

Dear Professors Lubinski and Scott,

Thank you very much for taking the time to review our manuscript entitled “Outcomes of screening and surveillance in people with two parents affected by colorectal cancers: experiences from the Familial Bowel Cancer Service” to be considered for publication in Hereditary Cancer in Clinical Practice. We have revised our manuscript based on comments provided by the Reviewers.

Please find our point-by-point reply below. All changes to the text of the manuscript are highlighted, with changes ‘tracked’ using Word. Please note that because of changes in the study group as proposed by the Reviewers, all of the results are slightly different from the initial submission, with individual numbers not specifically highlighted, though changes in interpretation or conclusions are highlighted.
Reviewer #2: An interesting manuscript. Good data in an individual with both parents affected by CRC are few and so new data in this area have potentially significant impact on screening recommendations.

Generally well written.

Reply: We thank the reviewer for the overall positive assessment and the opportunity to address the concerns that were raised.

Major concern:

I have major concerns regarding the study groups. The group representing those with both parents affected by CRC actually includes a number of individuals whose inclusion I think skews the data. This includes siblings with CRC (ie changing an individuals FHx from 2 first degree relatives with CRC, to 3 first degree relatives with CRC (including 2 in first degree kinship). This equates to a different risk group. Also included are those with advanced adenomas (although age not clear)…..if these are sibs with very young onset advanced adenomas, this also probably skews the risk too. I think to make the data clean and to allow for meaningful conclusions to be drawn, the authors need to limit the FHx to those with both parents affected by CRC ONLY - if there is additional FHx, then these to be excluded from the study group.

Reply: We acknowledge that the inclusion of siblings with CRC and advanced adenomas changes our registrants’ risk group and appreciate the reviewers suggestions on how to make the data cleaner and the conclusions more meaningful. Per the reviewer’s recommendations, we have re-analyzed our study group and presented the results after excluding the 3 registrants with siblings who had CRC. This exclusion is now reflected in the new results presented in all the figures and tables, as well as also now included in the “Exclusion criteria” and in the relevant Results and Discussion sections.

More minor concerns:

1. The description of "high risk" is difficult to follow. I assume that both parents equated to "high risk" in their surveillance protocol?

Reply: As described in the introduction, the Surveillance database in this study was started in 1980 as a risk management (surveillance) tool for registrants who were felt to be at higher-than-average risk for CRC based on varying family history, with multiple risk categories available. This included those in our study cohort who enrolled having a family history of both parents having been diagnosed with CRC.
The use of the term “high risk” in our manuscript (as opposed to “average risk”), however, reflects those definitions used in the different categories of relative risk based off of risk quantification by family history, according to the National Health and Medical Research Council (described in our manuscript under the Background section, paragraph 3):

“Risk quantification based on family history then places individuals in one of three categories of relative risk: Category 1 – those at or slightly above average-risk, Category 2 – those at moderately increased risk, and Category 3 – those at potentially high risk. The previous 2005 National Health and Medical Research Council [NHMRC]-approved clinical guidelines used quantification criteria which focused primarily on the identification of affected family members with young-onset (defined as before the age of 55) or those who have multiple affected family members on one side of the family tree. Those in Category 1 were recommended for average-risk screening, such as with iFOBT, as well as consideration of sigmoidoscopy, with colonoscopy only advised in symptomatic patients”

As noted in this paragraph, registrants in our cohort with both parents were – by the 2005 NHMRC definitions – originally in Category 1, and as such were only recommended for average-risk screening. We hope our manuscript helps make a case that registrants in our study cohort should be elevated above Category 1, so that they qualify for more intensive screening/surveillance strategies. Therefore, we agree with the recent 2017 updated NHMRC guidelines, as our study cohort would now be considered at least Category 2 (with two first-degree relatives with colorectal cancer diagnosed at any age) to “moderate” or “high” risk (in patients with at least one sibling with CRC).

2. "Average" is used as a statistical description....mean, median, mode? Also mean is often quoted - unless the data are normally distributed, this should be median.

Reply: We have edited our manuscript to clarify, so that “average” is corrected to “mean” when used as a statistical description. “Average” is now only used in the context of “average-risk” population. Histograms (not included with manuscript) of the different variables analyzed and included show a fairly normal distribution with mean = median in most cases.

3. Should an SSL of 10mm or more be included as advanced neoplasia? If dysplastic then maybe but if non-dysplastic perhaps more difficult to justify. This is particularly relevant as the authors compare risks to screening populations in their discussion and say they have found a higher risk of "advanced neoplasia" and use this as a justification for surveillance in this patient group. However the studies to which they make comparison generally report adenomas (Corley et al, Heitman et al); only the Bretthauer paper reports SSLs. Would the authors like to comment on FOBT being used as a means of detecting SSLs? Are there really robust data regarding this or
just good data for adenomas/cancer. The protocol includes FOBT screening but perhaps shouldn't be if they are looking to detect SSLs. Perhaps removing SSLs would provide better data for comparison with the literature OR separately describing advanced adenomas and advanced serrated lesions (SSLs >10mm or any size and containing dysplasia).

Reply: Upon further review, we agree with the convention of considering only SSPs with dysplasia as advanced neoplasia, due to our current understanding of the natural history of these lesions. Going back to primary data, we reviewed our SSPs, and as we found no dysplasia reported in the pathology for these patients, we have excluded them from our advanced neoplasia population for analysis.

5. At what age were the advanced lesions found - it is not clear. This will be an important determinant of age of onset of surveillance. The "mean" age at first neoplasm (not necessarily advanced) was 54 years. Can the authors provide justification for screening at the ages they recommend.

Reply: As the reviewer noted, the mean age of first neoplasm was 54, and the mean age of first advanced neoplasm finding was also 54 (Table 2). Given this and our understanding of the natural history of colonic neoplasms, we believe that colonoscopic screening should begin at least 5-10 years prior to the age of diagnosis in order to take advantage of the use of colonoscopy for the early detection and potential prevention of colorectal cancer through intervention on colonic neoplasms.

6. The data presented seem to indicate that the prevalence of CRC was the same as the average risk - is there therefore justification for treating this patient group differently from average risk? Furthermore, looking at their proposed surveillance for this group, can it be justified when the 2 cases of CRC were at ages 59 and 70 years??

Reply: We acknowledge the limitations of our study to comment on the prevalence of CRC given our small numbers, and also due to the fact that both of the cases were registered retrospectively. However, as noted in the comment above, we feel that the higher prevalence rates of neoplasms and advanced neoplasms in our study population show that there is a window of opportunity for the use of colonoscopy in the prevention of colorectal cancer through early intervention on colonic neoplasms.

7. Table 1 batches together colonoscopy and flexible sigmoidoscopy - clearly very different when it comes to surveillance! In addition there is no indication if any patients had CTC and if so what the results were.
Reply: For our study, we sought to capture endoscopic and pathologic results whenever possible. Upon further review of our primary data, 6 total flexible sigmoidoscopies were reported in 6 different patients and in whom all also had colonoscopies during their available screening and surveillance period. In these 6 flexible sigmoidoscopies, 5 had normal results, and only 1 was found to have a 4mm tubular adenoma. This patient then underwent a subsequent colonoscopy within 1 year that found an 11mm tubular adenoma. Therefore, in our population, including flexible sigmoidoscopies was not felt to alter our prevalence or incidence of neoplastic findings.

Regarding CT colonography, only one patient reported to have undergone one, and the result of that study was normal. We have now included a brief mention of this (Results section, paragraph 2):

“Given the time period of our study, computed tomography [CT] colonography was utilized by only one registrant, with reportedly normal study results.”

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Thank you very much for allowing us to revise and resubmit our manuscript for consideration. We hope that you find our revised manuscript acceptable for publication in Hereditary Cancer in Clinical Practice.

Jennifer Y. Pan, M.D., M.S.