Author's response to reviews

Title: Cost-effectiveness of family-history based colorectal cancer screening in Australia.

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Author's response to reviews: see over
Dear Editor,

We thank the reviewers for their comments, Please find below our detailed responses addressing all of their remarks and questions.

Regards,

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Response to reviewers’ comments

Reviewer #1

Please, include and discuss the absolute number of colonoscopies and the number of colonoscopies to save one-life from CRC death associated with the various strategies.

We have rerun the model as a microsimulation in order to provide estimates of the number of colonoscopies required to save one life as requested by the reviewer. We agree that this approach enhances the model and provides more specific estimates and outcomes. We have updated the methods and results sections as well as the tables and figure 2 accordingly. Please also see the end of the 5th paragraph of the discussion section.

Please include in the baseline or sensitivity analysis the possibility for 20-30% of CRC to arise de novo

We agree with the reviewer and have adjusted the model to take into account the proportion of CRCs developing with no preliminary lesion. Please see updated figure 1 and third sentence of the Model parameters section.

Please reconsider the relative level of adherence between i-FOBT and colonoscopy. It is not plausible a 40% equal adherence.

We used a 40% participation rate to iFOBT screening because it is the participation rate that has been observed for the Australian National Bowel Cancer Screening Program since its introduction in 2006. Regarding colonoscopy screening participation we agree with the reviewer’s comment. Table two provides the results of a sensitivity analysis for different colonoscopy screening participation rates. Please also see the second paragraph of the results section.
Reviewer #2

1. The starting age of family-history CRC screening is now assumed as 50 years old, and follow-up until 90 years old. According to the Australian National health and Medical Research Council guidelines, the starting age can be earlier than 50 years old for those with family history of CRC. A sensitivity analysis on the starting age should be evaluated, e.g. starting at age of 40 or 45. The upper limit of acceptable cost-effectiveness in the Australian health system is $50,000 per LYG. If the starting age is reduced to 40, it is unsure whether the screening strategies are affordable in Australia.

No reference is made in the Australian guidelines to an initiation of CRC screening at age 40 year. This applies to all three CRC risk categories defined in the guidelines.

The current NHMRC guidelines recommend colonoscopy screening every 5 years starting at age 50 years for people at “moderately increased risk” (category 2). This risk category is the focus of our analysis. We have expanded the discussion section to make this clearer (see beginning to the 5th paragraph in the discussion section). Our intent is also to present cost-effectiveness estimates of family history-based screening that are relevant within the context of the existing national programme which targets people from age 50 years. We modified the last paragraph of the discussion section to highlight this aspect of our analysis.

2. The study result can only be applied to Australia, as all assumptions and modelling parameters are purely based on the references from Australia figures. The title should be revised as ‘Cost-effectiveness of family-history based colorectal cancer screening in Australia’.

We agree with the reviewer and have modified the title accordingly.

3. The model assumed all CRCs developed from large adenomas, but it is possible the CRCs developed from small adenoma or even a flat adenoma. This should be highlight as a limitation in the discussion.

We agree. Please see our response to a similar suggestion from reviewer #1.

4. The authors suggested that all screening strategies to be cost-effective. What is the exact meaning of ‘cost-effective’? In my understanding on the Figure 2, biennial iFOBT is cost-effective than ten-yearly colonoscopy, as the running cost is cheaper, and the effectiveness on life-year gained is larger. Therefore, we should never recommend the ten-yearly colonoscopy. If budget is allowed, we can go for the five-yearly colonoscopy for extra benefit. As the concept of cost-effective in the manuscript is unclear, the conclusion of this study is not specific enough.
Our statement only intended to highlight the fact that the ICERs of all three strategies were substantially lower than the AU$50,000 threshold considered as the upper limit of cost-effectiveness in the Australian health system. However, we agree with the reviewer and have modified the second paragraph of the discussion section to avoid confusion.

5. Most of the assumptions are based on a health economics review in 2008 by Bishop J and a preliminary cost-effectiveness analysis in 2011 by Tran B. However, it is difficult to identify the source of parameters as the Bishop’s review included 71 tables and 30 figures. Columns for the sources of reference should be added in the Table 1 and Table 2, which can highlight the sources of reference. e.g. sensitivity of iFOBT: Table 20 of Bishop’s review. Are all of the references referred to the cases with family history of CRC? Clarification is needed.

We have modified tables 1 and 2 and provided the exact reference for each parameter in the model as recommended by the reviewer. We have also discussed the use of Bishop et al. study in the 8th paragraph of the discussion section.

Furthermore, data accuracy was randomly checked. The sensitivity and specificity of iFOBT for CRC were found in Table 20 of Bishop’s paper and reported as 52.6% and 87.2%, respectively. However, the sensitivity for CRC is reported as 0.479 in the table 1 of the manuscript. The explanation of the discrepancy should be addressed.

We did not use data from table 20 in Bishop et al for this study. Please see third column of table 1 for the exact references of the model parameters.

6. Some references should be added to support the writing of the Introduction. For example, no reference is given to the first sentence of the second paragraph: ‘Approximately 10-15% of all persons have a family history...were diagnosed.’; and the first sentence of the fifth paragraph: ‘Whilst three randomized controlled trials...’. In the first sentence of the sixth paragraph, another landmark paper should be quoted instead of the reference used in the reference 15. The author is the same and the paper is ‘Sonnenberg A, Delco F, Inadomi JM. Cost-effectiveness of colonoscopy in screening for colorectal cancer. Ann Intern Med 2000; 133:573-84. Besides, another cost-effectiveness analysis by Tsoi KK published in 2008 with reference to the Asia population should also be quoted.

We have included the references recommended by the reviewer.

7. The sensitivity analysis of ICER in table 5 can be plotted as a graph rather than presented as a table. It can enhance the visualization of your findings and make us easier to understand the main message from the sensitivity analysis. Similarly, the associated risk between CRC and the stronger family history in supplementary table 6-9 is also a sensitivity
It is worthwhile to consider the ways of summarized presentation, rather than the current formats in the detailed tables.

We believe that the detailed tables presented provide more information for the reader. The format in which the study results are presented has not been identified as an issue by reviewers 1 and 3.

8. The writing on the Markov Model methodology is too detailed. A brief model description with a figure of the decision tree is suggested.
We agree with the reviewer and have shortened paragraphs 1 and 2 of the methods section.

Minor Essential Revisions:
1. The results presented in the abstract are inconsistent with those presented in the main manuscript. For example, the average screening lifetime cost under the NBCSP scenario is AU$2,750 per person, but this figure is presented as AU$2,854 in the result and table 4. The inconsistency is also observed in the average lifetime expectancy. Checking for data accuracy is needed.

We have corrected all inconsistencies in the text.

2. In table 1, the parameters of the model included those aged under 50. If the model fits beyond the age of 50, these parameters can be removed.

We have removed the age category 45 – 49 from the table.

3. In the abstract, the ‘time’ is duplicated with ‘lifetime’ and should be removed in the last sentence of the Results. Proof-reading is suggested for the whole manuscript.

We have corrected all inconsistencies and typos in the text.
Reviewer #3

1) Overall study question and the methodology
- Cost effective analysis in the emerging field of CRC screening is an important question especially in increased risk individuals whereby more intensive screening has been recommended. This paper aims to inform the readers that “family-history based colorectal cancer screening” is cost effective. To make this statement sound, it is more valid to compare “family-history based screening” versus whole population screening instead of various screening methods in patients of moderate risk then make a final comment that the results are similar to other previous cost-effectiveness analyses, if not more cost effective.

Our model compares different family history-based screening strategies to the existing Australian National Colorectal Cancer Screening Program (NBCSP), which is the “Usual Care”/“base case” scenario of the model. In our model, the NBCSP is the “whole population screening” the reviewer refers to.

Currently, what the authors have done is to multiply the incidence of each transition state (e.g. adenoma and cancer rate) by 4 after referring to some published reference, then conclude that colonoscopy every 5 years is the most cost-effective option. Current rationale also needs discussion.
- Most published literature reported a 2-3 fold increased risk of CRC in those with a family history of CRC (John’s et al. 2001; Ng et al, 2013; Butterworth et al. 2006),

We have provided more explanations and justified our approach in the Model parameters section. Please also see paragraphs 3-5 in the discussion section.

whereas the authors have used a liberal estimate of 3-6-fold increased level of risk compared with the general population

These were not liberal estimates but the figures used in the current Australian CRC screening guidelines.

- What is the proportion of patients in the Australian population that have cancer diagnosed before the age 55 as this would be the single most important factor to determine if family-history based screening is cost effective (is it stated in the text?)

Screening strategies included in our model are addressed to people aged 50 years and older similar to the current NBCSP age criteria to which they are being compared.

- Why did they choose to start screening at the age of 50 in this group? Current guidelines suggest starting screening at 40 or 10 years younger than diagnosis of index case). If the authors target age 55 as the CA colon diagnosis age, the screening should start earlier in this increased risk group
50 is the age at which colonoscopy screening is recommended for people at “moderately increased risk” of CRC in the current Australian guidelines. Please also see our response to the first comment of reviewer #2

- How did they account for false negative screening results?

Screening test sensitivity and specificity are presented in table 1

2) Details on the methodology

Most studies generally select the discount rate of 3% - what is the rationale of selecting the discount rate per year of 5%

5% is the standard discount rate currently used by Australian health technology assessment agencies such as the Pharmaceutical Benefits Scheme

- They include screening until the age of 90 - isn’t this a bit too long?

We don’t think so. Previous studies analysing cost-effectiveness of risk-based CRC screening have used a similar age limit. See references 18 - 19

- For the cost of treatment of CA colon of different duke’s staging - they really cannot make that an average cost/ year, because usually, the cost of surgery or chemotherapy would be included in the first year than in the second year, and there should be a transition state called surveillance after that

This comment is difficult to address as it is unclear what exactly the reviewer is referring to. However, please note that CRC treatment costs used in the model take into account post-treatment surveillance costs. In our model, a person diagnosed with CRC can also recover and return to the population risk level.

3) Sensitivity analysis

- From the manuscript, the authors have included the compliance of screening and levels of CRC risks. Sensitivity analysis is performed to ensure that even if the % of a factor is largely deviated, the hypothesis or the statement still hold true. I believe a lot more factors need to be studied, including:

- Cost of colonoscopy, cost of FOBT - Proportion of population with a diagnosis of CA colon before the age of 55 - Age of start screening Only single factor sensitivity analysis has been performed in this study but not multiple factors

We do not believe that a sensitivity analysis of the cost of screening tests is relevant to the cost-effectiveness analysis of CRC screening, particularly in the Australian context where a national health safety net (i.e. Medicare) exists and covers all the population. Furthermore, the costs of screening procedures are determined by the providers and therefore the government (who would be
the organiser and payer for any potential family history-based screening) is unlikely to be able to modify those costs. Similarly, we think that a sensitivity analysis on the proportion of CRCs diagnosed before age 55 years in the population would not be relevant or particularly enhance our model, as there are no preventive or treatment actions that could rapidly modify the level of CRC incidence and mortality in the population.

**MINOR ESSENTIAL REVISIONS**

Page 6: Under screening programmes: Screening according “to” (missing word) the current....

We have addressed this mistake

*Only direct cost is included in this paper whereas the indirect cost e.g. productivity loss due to hospitalization, clinic visits, transportation have not been included, how about complication of screening and treatment of complication etc...*

This is stated as one of the limitation of our model

- *Utility is not used i.e. they only count the life year saved, but not QALY, although this is still considered acceptable*