Reviewer's report

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

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Reviewer: Kelvin K Tsoi

Reviewer's report:

The authors performed a cost-effectiveness analysis on the colorectal cancer (CRC) screening programme for the general population with family-history of CRC in Australia. The study concluded that the intensive colorectal cancer screening strategies targeting the increased risk population with family CRC history would be cost-effective. The sources of reference were mainly based on a publication with over 70 tables and figures, but it is unclear whether the references was only for those with family history of CRC.

Major Essential Revisions:

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.

2. The study result can only be applied to Australia, as all assumptions and modeling 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’.

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.

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.

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. 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.

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.

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 analysis. It is worthwhile to consider the ways of summarized presentation, rather than the current formats in the detailed tables.

8. The writing on the Markov Model methodology is too detailed. A brief model description with a figure of the decision tree is suggested.

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.

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. Besides, the table size can be reduced if it plots as natural history vs age groups in a 6x6 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.
4. The dollars were presented in ‘$’ or ‘AU$’. Clarification is needed.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.