Reviewer's report

Title: Exploring the Uncertainties of Early Detection Results: Model-Based Interpretation of Mayo Lung Project

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Reviewer: Ramon Diaz-Uriarte

Reviewer's report:

This paper might have provided an interesting study, complementing previous ones that exist along similar lines. But it suffers from a lack of clarity in explaining the context and a lack of details in the methods.

Major compulsory revisions

1. First of all, the authors say, without much explanation, that "(...) there was no reduction in lung cancer mortality among subjects in the intervention arms as compared to subjects in the control arm, but there was an increase in lung cancer survival" (p. 3). And in the abstract we are told "(...) demonstrated an increase in lung cancer survival, but no reduction in lung cancer mortality". Anyone not familiar with the Mayo Lung Project (MLP) will be left wondering what gives here. These statements seem to say "A and not-A". Since understanding the key findings of the MLP study is crucial to understanding this paper, this all needs to be explained more clearly. Summarizing quickly from the literature, we can say (for the sake of brevity I do not include details about the follow up periods to which these date refer, etc):

- There is no difference in lung cancer mortality between the screened and the control groups (in fact, there is a slight, but not statistically significant, larger lung cancer mortality in the screened group). The definition of what "lung cancer mortality" is can be found very clearly in, for instance, Marcus et al., 2000, "Lung Cancer Mortality in the Mayo Lung Project ..."

- There is a survival advantage for those diagnosed with cancer in the screened group compared to those diagnosed with cancer in the control
group. This is explained in detail, for example, in Marcus et al., 2000, "Lung Cancer Mortality in the Mayo Lung Project ...". JNCI and Flehinger et al., 1993, "Screening for Lung Cancer", Cancer.

- There is a larger incidence of cancer (i.e., number of cancer cases detected) in the screened group (all references say this explicitly).

- And, finally, if I remember correctly, there was a survival advantage, just plain, actuarial 5-year survival, for those in the screened group (Strauss et al., 1997, "Screening for Lung Cancer : Another Look", Chest).

Those papers, and others, show that we are not saying "A and not-A", since we are measuring different things. But this is not at all obvious from the current ms. Those papers, as well, give possible explanations of the results.

In fact, when the authors discuss the "key arguments from a modeling perspective", I'd say that they need to do a much more thorough job not just in terms of modeling perspective, but just in terms of the plain explanations of what might be happening. This reviewer finds some of the explanations of some of the above papers to be much clearer than the ones in the present ms. In addition, when exploring the key arguments, more detailed review of previously published papers should be provided, emphasizing the pros- and cons- of the different arguments and what the actual consensus (if any) is regarding each argument.

2. I would have liked to see more details about the MLP. For instance, I think that the control group participants received an annual set of screening tests, because that was the standard practice of the Mayo clinic in the 70s, but this is not said clearly in the current ms.

3. Page 4, second line, says "(...) morbid lesions or so indolent that patients". There is some type there but, more importantly, the idea of the indolent problem is not explained in this paper until a few pages later (p. 6, third paragraph). And this is a key idea.

4. Methods: we are given no references nor reasons for many of the modeling choices. This criticism applies to every single paragraph of
pages 5 and 6. I am not questioning the choices. But I would like to know why.

5. The first paragraph of the discussion is confusing. It is unclear whether you trying to explain the results of the MLP, or exploring the consequences of more sensitive screening. I understand that, ultimately, the objective is to explore the consequences of more sensitive screening, and you are using your model of the MLP to approach that question. But then, please say so. Start by explaining what your results say about the MLP, and then go into the bigger question.

6. Discussion: and how do your results compare to those from other similar exercises, including modeling ones? (See some of the references above).

7. Tables are currently part of the supplementary material, but they should be in the text, given their importance for the reported results. It is there where the parameters are shown, and the results reported. And, please, do not place suppl. mat. as word files when you can as easily provide a pdf.

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests