Reviewer's report

Title: Three myths about risk thresholds for prediction models

Version: 0 Date: 14 Aug 2019

Reviewer: Milo Puhan

Reviewer's report:

The paper by Wynants and colleagues is an educational paper about myths around risk categories and risk stratification based on prediction models. The paper is well written and I agree with the authors on the three myths and how they address them. It is very important that the paper emphasizes that prediction models only make sense and will ever be used if embedded in a sensible decision making context and if decisions are informed in a sensible and patient-centered way. The paper should be well accessible for clinicians and those with limited experience in prediction models and their use in practice whereas the issues are well known, at least among methodologists. BMC Medicine appears to be a good choice for such an article.

I would like to highlight just a few issues:

* Myth 2: Determining cost/value of each outcome is, as the authors say, of course key. I agree that reliable data on costs or utilities are often not available. It is possible to ask clinicians about this but there are two important caveats that should be mentioned. The way this cost/value is elicited from clinicians matters. This is not easy and the elicitation method appropriate for the question at issue should be used, and the (cognitive) burden for respondents considered. The paper should really not give the impression that one or few clinicians conveniently available could be asked rather informally and by some simple questions. Since the cost/weights matter so much this should be formally and using the best available methods. Secondly, and not less importantly, for many outcomes and decision making scenarios clinicians's view differs substantially from the patients' view (there are systematic reviews on this published in JAMA Internal Medicine) and the patients' view/preferences actually matters more in many decision making scenarios. It is often not sensible to have clinicians "false positives a health care professional would tolerate to find one true positive " since the patients' values and preferences matter ultimately. Thus please also refer to preference elicitation in patients or healthy people and not just to clinicians.

* A part that is rather implicitly addressed is how decisions work out in terms of outcomes (benefits, harms, cost) depending on the predicted risk. There are various components that come into play when modelling this depending on the effects of the intervention at issue for that particular outcome but also for all the other benefit and harm outcomes associated with the intervention. Often, the assumptions of outcomes in true positives, in false positives etc is too simplified. A way to address this is by benefit harm modelling that can also be used to determine risk thresholds on a group level (e.g. for developing recommendations) and on an individual patient level, depending on the outcome risks.
(again all benefit and harm outcomes of relevance), treatment effects and (average or individual) outcome preferences. An example for this is a recent paper in Annals of Internal Medicine on risk thresholds for when the benefits of statin for primary prevention outweigh the harms. I don't mention this that you cite our paper but analyses like that are actually the basis for determining at what risk an intervention or further test outplays the harms and then a the most suitable prediction model should be used (or developed and validated) to determine the individual risk as accurately as possible (see https://annals.org/aim/fullarticle/2717730/finding-balance-between-benefits-harms-when-using-statins-primary-prevention)

* The authors are top experts in the field and have published much. Nevertheless, the list of references refers a bit too often their own work and it may be good to reflect the literature a bit more broadly.

* Guideline does not appear to be the right category for this article.

Quality of written English
Please indicate the quality of language in the manuscript:

Acceptable

Declaration of competing interests
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

'I declare that I have no competing interests'
Statement on potential review bias
Please complete a statement on potential review bias, considering the following questions:

1. Did you co-author any publication with an author of this manuscript in the last 5 years?

2. Are you currently or recently affiliated at the same institution as an author of this manuscript?

If you can answer no to all of the above, write 'I declare that I did not publish with these authors in the last 5 years and also meet the affiliation criteria'. If your reply is yes to any, please give details below.

'I declare that I did not publish with these authors in the last 5 years and also meet the affiliation criteria

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal