Reviewer’s report

Title: A novel method for interrogating Receiver Operating Characteristic curves for assessing prognostic tests

Version: 1 Date: 14 Sep 2017

Reviewer: Mariska Leeflang

Reviewer's report:

The authors have addressed all my previous comments satisfactorily or mentioned good reasons why they haven't. However, they also changed the structure and text of the whole manuscript tremendously. Therefore, I have peer-reviewed the manuscript as if it was a new one.

I still think the whole manuscript could be improved on a more conceptual level, as sensitivity and specificity on their own are seldom used or reported for genuine prognostic tests; and for diagnostic tests, taking prevalence into account can be done without the nice graphs the authors show here; and researchers should realize that one cannot just combine sensitivity and specificity with any prevalence, as prevalence is linked to patient spectrum and therefore sensitivity and specificity do vary when prevalence varies. But maybe that would also make things more complicated. So I have just picked up on some details.

1. Page 10, lines 1+2: "low prevalence disease, high sensitivity and specificity can still be associated with (very) low post-test probabilities.". It is the first time this term is introduced in the paper and not really clear. Besides, this would only be true for the post-test probability of being diseased, not of being non-diseased. Why not only state PPV here?

2. The last paragraph of the results section seems to fit better in the Discussion section.

3. In line with my general comment, the statement on page 17, lines 1 to 3 ("equi-predictive value lines …. Partially - account for variation in patient spectrum") is not true in my opinion. As the authors explain further on, it only holds in the same setting and therefore probably in the same spectrum of patients. One just cannot apply a sensitivity and specificity or AUROC or LR or whatever measure found in a population with, say, a prevalence of 50% to a situation with for example a prevalence of 10%, as both populations will likely have different patient characteristics (the Willis and Hyde paper contains references to several papers around this topic). So to put it straight, I think the methods presented here do only hold if they are applied in a situation where the ROC curve was derived in a setting where the prevalence more or less matches the prevalence used to derive the equi-predictive value lines. I would like to see that addressed in the Discussion section.
4. I am not sure if I understand or agree with the statement made in lines 18 to 24. The authors state that use of NPV and PPV does not require calibration and that calibrated scores and predictive values have different use. But then the requirement for calibration has nothing to do with using equi-PV lines, right? And then the statement that no calibration is required is not helpful. Calibration is still required, as it serves a different purpose.


6. Page 19, lines 1 to 5: I do not understand these sentences. Particularly the link between being more sensitive to extreme disease and enhancing the transportability across different health care settings. Please elaborate and explain.

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