Reviewer’s report

Title: Quantifying the Added Value of New Biomarkers: How and How Not

Version: 1 Date: 05 May 2018

Reviewer: Michael Pencina

Reviewer's report:

The authors have been largely responsive to my comments but there are still a couple of issues that need to be clarified.

1. You seem overly positive on categorical NRI and overly negative on NRI at event rate.
   a. I would prefer that it is stressed more forcefully that categorical NRI should be presented separately for events and non-events.
   b. While it is true that the clinical interpretation of NRI(p) depends on the adequacy of the threshold, it's interpretation as a measure of distance between distributions of risk between events and non-events does not. In that sense reclassification from the null (AARD, Max Youden) is a global discrimination measure that corresponds to the AUC and it is proper. This should be noted.
   c. The fact that 28% have CVD risk above 3% does not necessarily mean that 3% is the wrong threshold. The AHA/ACC guidelines offer an optional threshold of 5% and some argue that statins could benefit individuals at an even lower risk.

2. You should state more clearly that discrimination slope and rescaled Brier are only asymptotically equivalent (and not equivalent). I still think it would be useful to give the authors a choice whether to base IDI on discrimination slope versus rescaled Brier noting the risks - slope being only asymptotically proper and rescaled Brier taking negative values.

3. Please add a citation by Hajime Uno to the section on AUC in survival - it provides the most elegant way to handle censoring.

4. Split sample validation based on one split is not appropriate. If you want to recommend this approach, ask for average of multiple splits.

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I am author of some of the metrics described

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