Reviewer's report

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

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Reviewer: Brian Willis

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Essentially the method proposed here relies upon treating the PPV and prevalence as mathematical parameters in order to define a straight line relationship between the sensitivity and specificity.

Thus for a given PPV and prevalence the locus of sensitivity of specificity pairs may be derived and follow a straight line. This idea is not new - Willis and Hyde do just this using the test positive rate and prevalence as the parameters to help define regions in ROC space for applicability (this should be acknowledged - J Clin Epidemiol 2014;67(5):538-46 and J Clin Epidemiol 2015;68(8):847-54 ). Here, the authors use the straight line relationships to define regions in ROC space where either the PPV and specificity criteria are satisfied or the NPV and sensitivity criteria are satisfied. In the example, they derive a region in which both of these are satisfied. The potential of the method would lie with test development as acknowledged by the authors.

Of course this depends on knowing the prevalence and deciding upon an acceptable criteria. What the authors fail to do in their analysis is to take into account the uncertainty in the estimates for the prevalence which are unlikely to be known accurately as assumed here. This would undoubtedly widen the permissible regions. The paper would benefit from including such an analysis.

Other points

1. Page 7 Line 9

Although there is no strict mathematical relationship between the sensitivity and specificity and prevalence, it is a myth to think that they are independent. Spectrum bias/effects demonstrates this clearly. Indeed a change of prevalence is often a crude marker for a change of patient spectrum which leads to a change of sensitivity and specificity of the test. As such this could potentially affect the AUROC.
2. Page 7 line 15 & 16

Probably better to say 'correctly identifying the "noise" from the "signal plus noise"'.

3. Page 9 Lines 4-6

Depends on what the screening test is being used for, and how serious the disease is. It may be that deciding upon an acceptable false negative rate first and seeing where the ROC curve crosses the sensitivity criterion may be the most appropriate approach to take in some cases.

4. Page 9 Line 9

See earlier point 1

5. Page 9 Line 14

This is just a rearrangement of Bayes' theorem and should be acknowledged as such. Further, both the specificity and sensitivity are fixed in Figure 2B, thus the likelihood ratio is fixed, and so it is illustrating PPV odds = LR x Prev odds (Bayes' theorem) - namely for a fixed LR the PPV increases with the prevalence.

6. Page 10 Line 9

Again this a rearrangement of Bayes' theorem and should be stated

7. Page 13 Lines 10-15

The 'rule-in' or 'rule-out' criteria really depends on the prevalence. The example shown in figure 5C, shows that setting the sensitivity >0.5 as the criterion is totally inadequate when the prevalence is 0.05. The corresponding PPV of 0.13 hardly rules in the condition. It is likely that the thresholds for sensitivity and specificity will depend on the prevalence or pre-test probability unless multiple testing is considered. This should be stated

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