Reviewer’s report

Title: Support of Personalized Medicine Through Risk-Stratified Treatment Recommendations

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Reviewer: Frederick Spencer

Reviewer’s report:

General comments: This manuscript is a good review of strengths as well as important deficiencies of some fairly high quality clinical practice guidelines. Strengths include pre-specified approach to data abstraction of clinical guideline characteristics and appropriate abstraction of fields/characteristics that are reflective of the clinical utility of such guidelines. The authors evaluate whether 20 existing guidelines provide risk stratified estimates of treatment effect, whether they transparently converted such estimates into absolute risks and benefits for different risk groups, and whether they incorporated patient preference. These are very important issues in guideline development which in the past has focused primarily on expert opinion.

A potential weaknesses of the study is the relatively strict selection/exclusion criteria - as the authors note this results in selection of relatively high quality guidelines - this limits generalizability. The vast majority of remaining guidelines are probably even more deficient in these areas. Nevertheless even the selected guidelines have considerable deficiencies which warrant discussion.

Specific comments:

Minor essential revisions:

1. Results, para 1 - "We identified 133 CPGs that made treatment recommendations . . . (Figure 2). This isn’t clear from figure 2 as the number 133 never appears.

2. Results - Figure 2 suggests that of the 719 guidelines reviewed only 60 did not use risk assessment tools. Obviously this isn’t true - it appears that articles were excluded for 1 of 4 other reasons prior to assessing this (?sequentially in the order they appear). So in reality there were probably many more of the 719 guidelines that didn’t provide risk assessment . This would be of interest to the reader as this is a major deficiency in most guidelines.

3. Discussion - while guidelines have found to be deficient in this paper in a number of ways it should also be pointed out that much of the time risk stratification tools for a disease state simply don't exist or are quite flawed. Sometimes even coming up with a representative baseline risk for specific outcomes - these are often derived from control arms of RCTs rather than from
well conducted observational studies (which can be difficult to find funding for as also difficult to publish).

Discretionary revisions

4. Discussion - The authors point out that most guidelines assume constant relative effects of a treatment across a risk spectrum - they suggest that this is less than optimal. I'm not sure that I agree with this - in most cases relative risk for a specific treatment for a specific outcome is constant across a risk spectrum. Is difficult to come up with examples where a therapy works less well (less platelet inhibition for example) in lower risk patients than higher risk patients.

5. Discussion - The authors suggest that varying relative effects could be derived for different at risk populations using patient-level data - this could be problematic. For example in some studies different relative risks are reported for different patient subsets post-hoc - it is not clear that these variations are real or due to play of chance.

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I have no competing interests.