Author’s response to reviews

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

Authors:

Tsung Yu (tsyu@jhsph.edu)
Daniela Vollenweider (danivollenweider@yahoo.de)
Ravi Varadhan (rvaradhan@jhmi.edu)
Tianjing Li (tli@jhsph.edu)
Cynthia Boyd (cyboyd@jhmi.edu)
Milo A Puhan (mpuhan@jhsph.edu)

Version: 2 Date: 5 September 2012

Author’s response to reviews: see over
Dear Editor
Thank you for the favorable evaluation of our paper. We think that the comments were very useful to revise this manuscript. Please find below a point-by-point reply to the reviewers’ comments.
We are looking forward to seeing your re-evaluation.
Sincerely,
Milo Puhan

Reviewer 1

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.

*We thank the reviewers for these general comments. We agree with the somewhat strict selection of guidelines and explain our revisions regarding the selection of guidelines below.*

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."

*We agree that this statement is not clear. During the review process, we identified 133 guidelines that were not excluded by the first 3 exclusion criteria (guidelines outside of US, Canada and UK NICE; guidelines on childhood disease; guidelines not about treatments). Of these 133 guidelines on treatments, we identified 20 that used risk assessment tools to make risk-stratified treatment recommendations. We made changes in the revised manuscript to clarify this.*

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.

We agree that it would be interesting information to know how many guidelines recommend making a risk assessment. However, we did not extract this information for guidelines that were unrelated to the diseases considered in this study. But as explained above, 20 guidelines do make risk-stratified treatment recommendations out of 133 guidelines that make any kind of treatment recommendations for the diseases we considered in our study. We made changes in the revised manuscript to clarify this.

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).

We fully agree with the reviewer and added to the discussion the lack of validated risk assessment tools for some diseases and settings.

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. It 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.

This is a controversial issue. Some studies indicated that treatment effects are fairly constant across the risk spectrum while others did not. It is currently difficult to say if there is insufficient evidence about constant relative effects. We agree that our statement may be too skeptical and toned it down in the revised paper.

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.

We agree that this is challenging to assess. On the other hand, such approaches would provide some sensitivity analyses to test the assumption about constant relative treatment effects. In the revised paper, we refer to these approaches as sensitivity analyses.

Reviewer 2
Title: Please identify as a systematic review or environmental scan
We hesitate to call our study a systematic review since we did not search many databases nor had the intention to identify all CPGs. Instead, our goal was to analyze a subset of CPGs that are likely to have a substantial impact on patient care. Reviewing definitions for environmental scans (e.g. http://cadth.ca/products/environmental-scanning/environmental-scans) we believe that this term is more appropriate.

ABSTRACT
Please consider adding: inclusion criteria for CPG, data analysis strategies

We are not sure what information should be added to what we already have in the abstract since the major criteria are already there and since we did not use any statistical tests or modeling. But we did add that CPGs had, to be included, to make risk-stratified treatment recommendations based on risk assessment tools.

Not clear what the objective is: the authors stated: to assess how CPGs develop risk-stratified treatment recommendations for the prevention or treatment of common chronic diseases but I think the objective should be reframed as: to identify if eligible CPGs include risk-stratified treatment recommendations; if they don’t, then the “how” makes no sense. Clearly the authors identify CPGs first.

We agree that the objective is not stated clearly. We revised the objective according to the more precise objective stated at the end of the introduction section. In the revised abstract we say that we assessed whether or not CPGs make risk-stratified treatment recommendations and, if they do, how these recommendations were developed.

We made the abstract more consistently in active voice wherever possible.

INTRODUCTION
It would be a stronger argument if the authors could cite a study that showed that risk-stratified treatment recommendations for the prevention or treatment of common chronic diseases has been shown to have favourable outcomes on process of care or patients outcomes. If yes, then it makes a lot of sense to identify if CPGs include risk-stratified treatment recommendations.

We agree and included several references in the introduction that support favorable outcomes based on risk-stratified treatment (compared to treatment not informed by risk prediction).

Is risk assessment tool the same as risk stratified treatment recommendations? I would suggest keeping the same terminology throughout the paper. Under methods section, inclusion criteria focus on risk assessment tool.

No, they are not the same. A risk assessment tool is used to predict the outcome. Based on that prediction and specific treatment threshold, the risk stratified treatment recommendations
suggest whom to treat or not to treat. We tried to clarify this throughout the paper and to be consistent with terminology.

Specify study characteristics
This is not clear. The authors stated: We included CPGs that recommended using risk assessment tools to inform treatment decisions. However, under the abstract section they conclude: Only a small proportion of CPGs for chronic diseases make risk-stratified treatment recommendations with a focus on heart disease and stroke prevention, diabetes and breast cancer. Therefore, it seems as though their inclusion criteria were: 1) include risk assessment tool; 2) chronic disease limited to CVD and DM (?) Is risk assessment tool the same as risk stratified treatment recommendations? I would suggest keeping the same terminology throughout the paper.

This comment refers to the comment just before and to the confusion about the aim we may have created in the abstract. In the revised paper, we kept the terminology for risk assessment tool and risk stratified treatment recommendations consistent and made it clear that we assessed those (relatively few) CPGs that do make stratified treatment recommendations based on a risk assessment tool.

Information sources
Please consider moving before inclusion criteria

As suggested, we moved the section on information sources before the eligibility criteria.

Data items 11 Ok but a table with each item and a clear definition would be appreciated

We appreciate this comment but we prefer keeping the text because we do not see how a table would add much information. Also, we believe that the tables (1 and 2) with the actual data from the CPGs illustrate the content of the data items better than a table with just a description of the data items.

Risk of bias in individual studies
There is no clear section on quality assessment related items pertaining to the risk assessment tool

Our study actually aimed at the assessment of the methodology that CPGs used to develop risk-stratified treatment recommendations. As such, the data items we extracted represent the quality assessment. We do not think that a risk of bias assessment of individual would be informative in this study since we were interested in the type of studies considered to develop risk-stratified treatment recommendations (e.g. observational studies, RCTs, meta-analyses, patient preference surveys) and how they were combined (e.g. risk prediction and treatment effects) rather than in the specific evidence base for each clinical area.