Reviewer's report

Title: Old drugs, old problems: Where do we stand in prediction of rheumatoid arthritis responsiveness to methotrexate and other synthetic DMARDs?

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Reviewer: Paco MJ Welsing

Reviewer's report:

The authors report on a review to summarize the currently available data on predictors of response to MTX and other, to discuss the causes for discrepancies in results reported and to critically analyze the possible translation into clinical practice. The question regarding prediction of treatment response is not very new. Also in the context of current T2T treatment paradigms and wider dose adjustments used with MTX/DMARDs as opposed to biologicals and efficiency/cost-effectiveness reasons, a focus on biological treatment for this question might be more helpful (but not newer). This should be discussed. My main concerns are the lack in clarity in the methodology of the literature review and methods on summarizing the evidence. Although this last point is difficult due to different approaches and study designs of individual studies, this is key to optimal interpretation of the body of evidence to my opinion. It seems a narrative review and although nicely written the conclusions are not very new and use of these results for clinical practice (or future research) are limited to my opinion.

- Major Compulsory Revisions

1) A methods section regarding the review (i.e. search strategy, inclusion/exclusion criteria for papers etc) and methodology regarding how results are abstracted and summarized. This is a difficult task given the inherent multivariable nature of prediction studies and differences in individual study designs. However to my opinion this is key to optimal use of a (systematic) review on this issue.

2) The review seems mainly narrative. The tables as present in the paper are not referenced throughout the text. Probably the tables could also be more informative, for example concerning other variables studied (multivariate analysis) in the (individual) papers. Some more quantitative summary might be helpful. Results seem an (subjective) opinion of the authors.

3) No statistical results are mentioned. Although very difficult a more quantitative summary of the result might greatly improve the paper to my opinion.

4) Abstract does not report on any results/conclusions from the review.

- Minor Essential Revisions

1) Due to the nature of the review there is (too) much text, although well written (some small ‘typos’) maybe referring more to tables and some more quantitative
tables (see earlier comments) might improve the readability.

2) A discussion on the distinction in studies on prediction of response to MTX/DMARD and biologicals is needed. Also in light of current treat to target treatment strategies and fast increase in treatment intensities to (biological) treatment.

- Discretionary Revisions

1) Figure 1 is not really useful in context of predicting MTX/DMARD response in clinical practice (which is the main objective of the paper)

2) Division of possible predictors in clinical, nongenetic biomarkers and genetic biomarkers might be counterintuitive. No single predictor is probably sufficient for response prediction in clinical practice. Therefore especially a combination of different predictors (irrespective of type of predictor) is of interest. The authors should at least discuss what/which combinations of predictors might have suitable predicting ability and how they can be used in clinical practice (i.e. when to make the decision not to start with MTX/DMARD treatment)

**Quality of written English:** Needs some language corrections before being published

**Declaration of competing interests:**

No competing interests