Author’s response to reviews

Title: Clinical Decision Support System for the Management of Osteoporosis Compared to NOGG Guidelines and an Osteology Specialist: A Validation Pilot Study

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Responses to reviewers' comments

Reviewer 1:

Major:

1. Neither this paper nor the referenced 2015 paper indicates how OPAD generates 10 year fracture risk estimates. Was the OPAD model and its parameter coefficients developed and then validated in specific cohorts? If not, are the fracture risk estimates based on FRAX? In that case high correlations between OPAD and FRAX 10 year fracture risk estimates are just a confirmation of a tautology.

Thank you for this important question. In this context, FRAX have not published their statistic epidemiological methodology concerning their 10-risk calculation. We do not use classical epidemiological relative risk calculation, instead as we descript in our paper from 2015, we use “Intellix Advisor” which is a knowledge mapping approach where expert knowledge and various public data (including those epidemiologic studies that have been using FRAX for their risk calculations) to construct a neural IT network-based model to estimate individual fracture risk based on clinical findings. We have chosen to compare our risk-outcomes with FRAX as it is considered the gold standard of osteoporosis risk calculation. In this context we are working on including information on reduction of height, history of falls and hopefully we will also be
able to implement in to our OPAD system individual genotypes – but we are too early on that road. We have expanded this discussion in the background part of the manuscript.

2. When I check the Expeda website, it appears that OPAD is a commercial technology. Are the fracture prediction model parameter coefficients proprietary information? If so this should be acknowledged.

Expeda is a partly commercial research start-up company, but all development to date has been made under the cover of The University of Iceland and Reykjavik University. The OPAD system is open for use for all Icelandic physicians, both at the National University Hospital and for general practitioners, but the OPAD-neural-network-model is currently proprietary. We have included this information in the background part of the manuscript.

3. Related to 1 and 2, the correlation between FRAX and OPAD seems less important than how well OPAD predicts fracture in specific populations. While I appreciate that OPAD goes well beyond FRAX by also incorporating additional covariates and making treatment and other management recommendations (and yes this is important), these recommendations are based on the fracture risk estimates, and hence the calibration of the models and how well the OPAD model discriminates between those who will and those who will not fracture is critically important information. I would think any health care delivery system would want to know this before considering implementing this product.

We want to thank the reviewer for this very relevant question. As the reviewer rightfully points out, ideal validation of a fracture risk model would include a full external validation in the at-risk populations, and it is certainly one of our next-steps forward in the development of the OPAD, but it is beyond the scope of our present study where we have emphasized on the treatment recommendations. Most clinicians in the field of osteoporosis management are in consensus that FRAX is currently the best validated and most widely accepted risk estimation tool for calculating 10-year risk of osteoporotic fractures. This is further evident by its incorporation into over 100 worldwide clinical guidelines on osteoporosis management. As a first step in verifying the risk estimation OPAD, we have opted to compare our model to this current “gold standard” of FRAX. In light of the very have high correlation to FRAX with only a slight bias toward overestimating risk (1.8%), authors feel confident that the treatment recommendations are based on accurate risk estimates, until we can evaluate OPAD’s performance in a dedicated cohort study.
Minor:

1. While the authors emphasize the similarity of treatment recommendations between expert opinion and OPAD, OPAD recommends treatment in an absolute 16% additional patients. For those 16%, what proportion were referred for specialist evaluation, and what proportion did the discrepancy seem to be attributable to higher estimated risk of fracture with OPAD vs FRAX?

   • We appreciate your question. As the reviewer points out, cases where OPAD refers expert opinion are classified as “treatment” in the Venn diagrams. We have looked further into this group of n = 23. In the majority of cases (17 of the 23 cases (74%)) the OPAD referred the cases for expert opinion. The remaining 6 cases can be explained by overestimation of OPAD’s risk estimation. That is an absolute of 4% resulting from OPAD’s overestimation in risk. We have clarified this in the discussion section of the manuscript.

2. Weren’t the recommendations of NOGG intended to be specific for the UK population? Or is NOGG being used in Iceland currently in clinical practice? If not, I am not sure of the relevance of comparing OPAD recommendations to NOGG. In contrast, the comparison of Icelandic osteoporosis expert recommendations and those of OPAD would seem to be highly relevant.

   • Thank you for raising this question. No current clinical guidelines incorporating 10-year fracture risk assessment exist in Iceland, so practitioners commonly rely on established international guidelines from organisations such as NOF, NOGG or the ESCEO. The NOF guidelines recommend the use of a fixed intervention threshold which must be based on country-specific health economics / cost-utility analysis. Age-dependent interventional threshold can be seen as more independent, and can be used in countries where FRAX models is available, including Iceland. This interventional threshold strategy was first introduced by NOGG, but later adopted into the European (ESCEO) guidelines. The reason for the authors opting to compare to the NOGG guidelines instead of the current ESCEO is that the average fracture incidence in European countries (EU-27) is significantly lower among the younger age groups than in the Icelandic population, which resembles much better the UK population which also has higher fracture rates among younger post-menopausal females. [1,2]

3. Page 10, lines 5 through 8. I am not sure what the authors message is here. This is phrased as though the similarity of OPAD if BMD is included compared to when BMD is not
included is an advantage of OPAD. If so, I do not buy that argument. If the FRAX fracture risk estimates with and without BMD differ by each other by only 1.8%, they too are quite similar.

• Authors agree with the reviewer's criticism that the difference between OPAD and FRAX is small and the paragraph has been adjusted accordingly in manuscript.

Reviewer 2

The introduction section is too long and can be shortened.

I believe the first and second paragraphs can be removed or summarized, as the audience for this manuscript can be assumed to be familiar with the definition of osteoporosis, and the WHO description and diagnostic criteria has been repeated multiple times in literature.

Instead, I would like to invite the authors to more deeply focus on the gap in the current clinical management of osteoporosis and what is missing that they are trying to solve.

Please provide some direction and recommendations for additional research given your study findings.

• We thank you for valuable suggestions.
• Introduction has been shortened, first few paragraphs summarised.
• We have added more detail on current problems with risk-assessment and osteoporosis management
• Authors hope to report on a more robust prospective validation study of the OPAD system in the near future. Discussion section extended to include further development and validation of OPAD