Risk Analysis of Prostate Cancer in PRACTICAL Consortium—Reply Letter

Ali Amin Al Olama[1], Rosalind A. Eeles [2, 3], Zsofia Kote-Jarai[2], Douglas F. Easton[1]

[1]Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, UK. [2]Institute of Cancer Research, London, UK. [3]Royal Marsden National Health Service (NHS) Foundation Trust, London and Sutton, UK.

Financial Support: D.F. Easton was recipient of the CR-UK grant C1287/A10118. R.A. Eeles was recipient of the CR-UK grant C5047/A10692.

Corresponding Authors: Professor Douglas F. Easton, Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, UK. Email: dfe20@medschl.cam.ac.uk, Telephone: +44 1223 748629, Fax +44 1223 748628; And Dr. Ali Amin Al Olama, Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, UK. Email: aa461@medschl.cam.ac.uk, Telephone: +44 1223 748638, Fax +44 1223 748628.

Disclosure of Potential Conflicts of Interest: R.A. Eeles has received speakers bureau honoraria from Succinct Communication and medical education support from Janssen. No potential conflicts of interest were disclosed by the other authors.

Word Count: 394

We thank Martens et al. for their comments on our paper.

We agree that calibration of the model in the extremes of the risk distribution is important. We observed (1) , however, that that the estimated odds ratios for men in the top and bottom 1% of the risk distribution (4.2 and 0.14 respectively) did not in fact differ from those predicted under a model with a continuous (log-additive) effect of the PRS on risk (3.8 and 0.20 respectively). In addition, formal calibration tests showed no evidence of departures from the log-additive model (P=0.12 by Hosmer and Lemeshow test).

In our data, the AUC was 0.63 (95%CI 0.62-0.64) for a model incorporating age and family history, and this rose to 0.69 (95%CI 0.68-0.70) when the polygenic risk score was incorporated. The AUC cannot, however, be compared directly with other models such as the PCPT model, which is based on measurement PSA and DRE and predicts the risk of prostate cancer detection on biopsy. Our model is based solely on genetic data and predicts the subsequent risk of prostate cancer. Clearly, if PSA level were also incorporated into the model, the AUC is likely to be higher. We also note that the AUC is likely to increase as additional SNPs are identified. For example, a recent study using data on 65 SNPs estimated an AUC of 0.68 (2). Finally, it is worth noting that the AUC is not necessarily a good measure of the predictive value of a model, and that other measures such as the net reclassification index may be more useful.

We agree that the discrimination of risk prediction models may be overestimated in the dataset in which the model was developed, due to overfitting. To address this, we re-estimated the model parameters in a random sample of the dataset that included 90% of the cases and controls. The polygenic risk score from this model was then tested on the remaining 10% of the dataset. The odds ratio per 1 standard deviation of the PRS was 1.74 (95%CI 1.60-1.79) in the training set and 1.60 (1.49-1.73) in the validation set. Thus, PRS remains highly predictive of risk in the validation dataset, but there is some suggestion of overfitting. Further validation of polygenic risk scores based on all available SNPs, in independent datasets, will be important before such scores can be used routinely.

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