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CORRESPONDENCE

Genetics and Genomics

Response to: Genetic risk scores may compound rather than solve the issue of prostate cancer overdiagnosis (BJC-LT3342090)

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We thank the authors Horton et al. [1] for their comments on our recent paper about the potential application of a genetic risk score for prostate cancer detection in primary care settings [2]. We agree that the evidence base is not yet strong enough to support the use of genetic risk scores in clinic, although we would argue that Conti et al.'s GRS for prostate cancer [3] is reasonably, not weakly, predictive with an AUC of 0.703 when applied in our study.

The authors cite a study by Klein et al. as evidence that 'PSA is more predictive of prostate cancer metastasis or death than a genetic risk score' [4]. Klein et al. applied a risk score including 125 SNPs to two screening (asymptomatic) cohorts; the outcome was lifetime distant metastases or death from prostate cancer. In that study, the AUC of a single PSA test was 0.78, and the AUC of the GRS was 0.63. The AUC of GRS alone in our study was 0.703; the difference could be explained by the inclusion of a greater number of SNPs in the Conti score or the differences in study population. Crucially, our study included men with lower urinary tract symptoms and the outcome was prostate cancer within two years; this is different to the screening population.

The problem of false positives does deserve attention. The specificity of PSA is estimated at around 0.20; only one in five men who do not have prostate cancer will have a negative PSA test [5]. We hypothesise that combining GRS with PSA in clinic could reduce false positive referrals from primary care. Careful consideration of the appropriate threshold for an integrated risk model would be needed to ensure that more men are not '*swept along a pathway of ultimately unnecessary invasive investigations*'. Currently, men who are referred get a pre-biopsy MRI, reducing the risk of unnecessary invasive investigations by 30–60%. This approach is less likely to find indolent prostate cancer. Changes in prostate biopsy from trans-rectal ultrasound to trans-perineal reduces risk of biopsy complications, and only 4% of men with indolent disease in the UK are over treated [6, 7].

The lack of ethnic diversity in our study remains a significant barrier for this and all research using the UK Biobank as a resource. Greater testing and evaluation of the use of GRS in primary care is needed to ensure that this approach results in health benefit, without increased risk of harm.

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SB drafted the response. All authors reviewed before submission.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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