Re: Polygenic risk scores for pre-MRI risk stratification in men with clinically suspected prostate cancer

Amit Sud[1,2], Richard S. Houlston[2]

1. Department of Medical Oncology, Dana-Farber Cancer Institute, 450 Brookline Ave, Boston, MA, USA.
2. Centre for Immuno-Oncology, Nuffield Department of Medicine, University of Oxford, Oxford, UK.
3. Division of Genetics and Epidemiology, The Institute of Cancer Research, London, UK

Correspondence: Amit Sud, amit_sud@dfci.harvard.edu, +1 877-442-3324

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We read the article “Polygenic risk scores for pre-MRI risk stratification in men with clinically suspected prostate cancer” with interest(1). We wish to highlight key methodological limitations and note that several conclusions are not supported by the presented data.

A fundamental limitation is the choice of outcome. The study evaluates associations between prostate cancer polygenic risk scores (PRS) and MRI (PI-RADS) rather than histologically confirmed significant prostate cancer. PI-RADS scores are an imperfect surrogate and are not equivalent to a cancer diagnosis, nor to treatment-relevant disease. Lacking biopsy or follow-up data, the manuscript provides no evidence that PRS improves detection, reduces missed significant disease, or safely identifies men for MRI deferral.

Accepting this limitation, the study suffers from significant collider stratification bias(2), as evidenced by the finding that PSA alone showed no association with MRI positivity. By restricting the cohort to "cancer-suspected" men, the authors conditioned on PSA levels. This explains the limited performance of the baseline clinical model, which performed no better than chance (AUC≅0.50). Comparing the PRS model against this compromised baseline exaggerates the incremental value of the genetic score.

The reported statistical associations are modest. The PRS explains only 5–6% of variance in MRI outcomes, consistent with PRS capturing broad population-level susceptibility rather than clinically actionable individual risk. Model performance undermines the authors’ claims; the genetic model’s discrimination remains weak (AUC≅0.67, which equates to a sensitivity of 69% and false-positive rate of 34%). Moreover, at a high-sensitivity threshold (91%), adding PRS to the standard clinical model increased the false positive rate from 85% to 88%, reflecting the poor risk discrimination afforded by PRS and noise inherent to a small, single-centre hold-out set with overlapping confidence interval. Given these limitations, claims of improved efficiency based on decision curve analysis are thus speculative without outcome-based validation. Furthermore, invoking screening studies like BARCODE1, which has inferior performance when compared to PSA(3), further highlights the challenges of implementing PRS in clinical care.

Finally, clinical metrics confound the reported associations. PSA density, which outperforms the PRS-based models and in this context likely identifies men with benign prostate hyperplasia, was excluded from the primary analysis. Additionally, the MRI-negative group was significantly enriched for men with a prior negative biopsy (28% vs 11% $P = 8.7 \times 10^{-5}$), a strong predictor of

benign disease. The exclusion of these powerful clinical predictors from the primary analysis is difficult to justify and highlights the limited value of PRS once relevant clinical information is considered.

Taken together, this study demonstrates little more than a weak association between PRS and an intermediate imaging outcome. The data do not support the manuscript's claims of clinical utility, safety, or readiness for implementation. More broadly, it is highly questionable whether such PRS associations will ever translate into meaningful clinical decision thresholds, especially in the context of downstream diagnostic settings(4,5). We believe the conclusions should be substantially tempered, and that this publication risks promoting premature adoption of PRS in diagnostic pathways without demonstrable patient benefit.

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