# Polygenic risk scores may miss the mark when predicting aggressive prostate cancers

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According to a research letter published in *JAMA Internal Medicine*, prostate cancer screening frequently results in biopsies that find clinically insignificant cancer or no cancer at all.

A polygenic risk score (PRS) can measure the disease risks associated with genetic variants that an individual carries, and there is clinical interest in using these gene-driven scores to improve risk prediction for prostate cancer. Still, the current letter cautions, reliance on the method could cause unnecessary procedures and underestimate risk prediction for aggressive prostate cancers.

Vanderbilt University Medical Center and Stanford University researchers looked at the genes of 655 men without prostate cancer, median age of 63, who underwent a prostate biopsy. Each man was assigned a polygenic risk score (PRS) based on the weighted sum of 269 genetic variants associated with prostate cancer in an assessment called $PRS_{269}$.

Researchers focused on two outcomes: any prostate cancer vs. no cancer, and grade 2 or higher prostate cancer vs. no cancer or grade 1 (insignificant) cancer. Multivariable logistic regression compared the $PRS_{269}$ to a standard clinical predictor (Prostate Biopsy Collaborative Group) and biopsy outcomes.

Prostate cancer (any type) was identified on biopsy results in 341 (52%), and 176 (27%) had grade 2 or higher cancer. The $PRS_{269}$ was successfully associated with finding cancer (any type) on biopsy but was not better than the clinical assessment at predicting grade 2 or higher.

The finding supports the conclusions of previous research papers by members of the current research group. One previous paper, based on a study led by current team member Linda Kachuri, assistant professor of Epidemiology and Population Health at Stanford, found that genetic screening techniques alone resulted in "...overdiagnosis and overtreatment of clinically insignificant tumors." Kachuri and others have published work that finds similar results in breast cancer.

According to the article in *JAMA Internal Medicine*, while $PRS_{269}$ improved model discrimination for all cancers, it was still less than other validated prostate cancer biomarker predictors such as the Prostate Health Index. The study articulates the need to rely on the most effective prediction tools for aggressive prostate cancers, as failing to do so could be fatal.

**More information:** Kerry R. Schaffer et al, A Polygenic Risk Score for Prostate Cancer Risk Prediction, *JAMA Internal Medicine* (2023). DOI: 10.1001/jamainternmed.2022.6795

Robert J. Klein, Bringing Prostate Cancer Polygenic Risk Scores to the Clinic, *JAMA Internal Medicine* (2023). DOI: 10.1001/jamainternmed.2022.6782