

## GenProb-PCSM: Germline Risk Stratification for Lethal Prostate Cancer Across Ancestry Groups

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**Background:** Germline genetic factors are increasingly recognized as predictors of prostate cancer (PCa) risk, but their utility for predicting lethal disease after PCa diagnosis and their performance across ancestry groups remain less established. We recently developed and published GenProb-PCSM, a simplified weighted germline score integrating pathogenic variants and common genetic variants associated with prostate cancer-specific mortality (PCSM).<sup>1,2</sup> Here, we evaluated the association of GenProb-PCSM with lethal PCa in the overall population and separately among men of European and non-European ancestry.

**Methods:** The analysis included 14,043 UK Biobank participants with localized PCa at diagnosis, among whom 2,186 subsequently experienced lethal PCa phenotypes, defined as PCSM and/or metastatic progression. GenProb-PCSM was evaluated using predefined low-, intermediate-, and high-risk categories. Time-to-event analyses used age as the time scale with delayed entry at PCa diagnosis. Analyses were performed in the overall cohort and stratified by European and non-European ancestry.

**Results:** Among 14,043 men with localized PCa, 2,186 developed lethal PCa phenotypes. GenProb-PCSM classified 85.8% of men as low risk, 12.9% as intermediate risk, and 1.4% as high risk (**Table**). Compared with low-risk men, those classified as high risk had a substantially increased risk of lethal PCa (HR=3.11, 95% CI 2.42–3.99;  $P<0.001$ ). Risk stratification was highly consistent among 13,366 men of European ancestry, with 13.2% classified as intermediate risk and 1.4% as high risk; high-risk men had a 3.09-fold increased risk of lethal PCa (95% CI 2.39–4.00). Among 677 men of non-European ancestry, 6.2% were classified as intermediate risk and 1.5% as high risk. Despite the smaller sample size and only 83 lethal events, high-risk men had a 2.95-fold increased risk of lethal PCa (95% CI 1.02–8.57;  $P=0.046$ ). Cumulative incidence curves demonstrated clear risk separation across GenProb-PCSM categories in both ancestry groups (**Figure**).

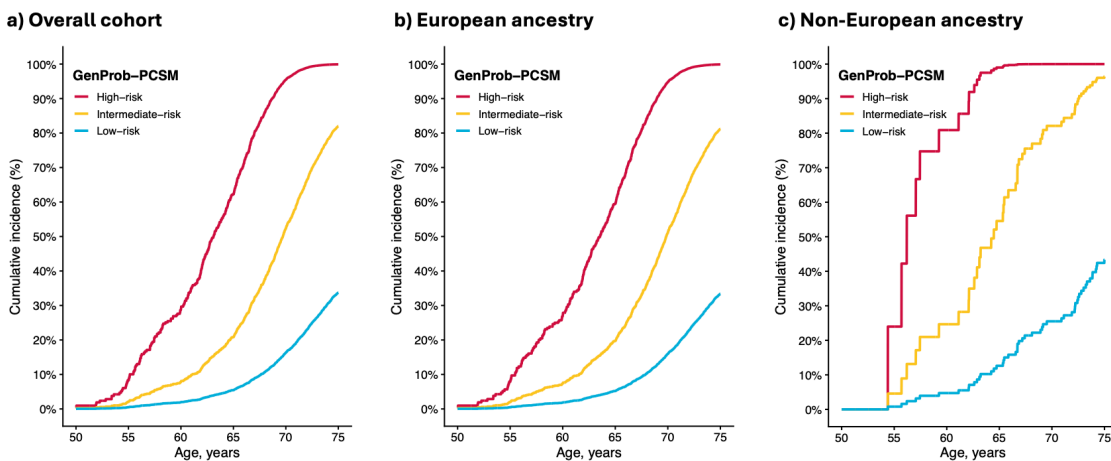
**Conclusions:** GenProb-PCSM identifies men with substantially different risks of lethal PCa phenotypes after diagnosis, with remarkably consistent effect estimates in European and non-European ancestry groups. Germline risk stratification may complement clinical and tumor-based prognostic factors to improve identification of men at increased risk for lethal PCa.

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**Conflicts of Interest Disclosure Statement:** Endeavor Health has agreements with GenomicMD and GoPath Diagnostics for genetic tests of polygenic risk scores. J. Xu serves a scientific advisory board member for GoPath Diagnostics and GenomicMD.

**Table. Association of GenProb-PCSM with lethal PCa phenotypes across ancestry groups in UK Biobank**  
**Lethal PCa phenotypes (PCSM and/or metastatic progression)**

|                              | Subjects, No. (%)     | Lethal PCa, N. (per 100,000 person-year) | HR (95% CI)      | P-value  |
|------------------------------|-----------------------|------------------------------------------|------------------|----------|
| <b>Overall cohort</b>        | 14,043 (100)          | 2,186 (1962.93)                          |                  |          |
| GenProb-PCSM, per SD         | .                     | .                                        | 1.15 (1.11-1.18) | <1E-300  |
| Low-risk                     | 12,043/14,043 (85.76) | 1,766 (1828.51)                          | 1.00 (ref)       |          |
| Intermediate-risk            | 1,810/14,043 (12.89)  | 350 (2576.91)                            | 1.35 (1.21-1.52) | 2.50E-07 |
| High-risk                    | 190/14,043 (1.35)     | 70 (5830.66)                             | 3.11 (2.42-3.99) | <1E-300  |
| <b>European ancestry</b>     | 13,366/14,043 (95.18) | 2,103 (1984)                             |                  |          |
| GenProb-PCSM, per SD         | .                     | .                                        | 1.15 (1.11-1.18) | <1E-300  |
| Low-risk                     | 11,418/13,366 (85.43) | 1,694 (1849.06)                          | 1.00 (ref)       |          |
| Intermediate-risk            | 1,768/13,366 (13.23)  | 343 (2589.14)                            | 1.35 (1.20-1.51) | 5.20E-07 |
| High-risk                    | 180/13,366 (1.35)     | 66 (5809.16)                             | 3.09 (2.39-4.00) | <1E-300  |
| <b>Non-European ancestry</b> | 677/14,043 (4.82)     | 83 (1546.74)                             |                  |          |
| GenProb-PCSM, per SD         | .                     | .                                        | 1.15 (1.01-1.31) | 0.04     |
| Low-risk                     | 625/677 (92.32)       | 72 (1449.52)                             | 1.00 (ref)       |          |
| Intermediate-risk            | 42/677 (6.2)          | 7 (2092.34)                              | 1.52 (0.70-3.28) | 0.29     |
| High-risk                    | 10/677 (1.48)         | 4 (6209.86)                              | 2.95 (1.02-8.57) | 0.046    |



**Figure.** Cumulative incidence of lethal prostate cancer according to GenProb-PCSM risk category, overall and by ancestry. Cumulative incidence of lethal prostate cancer, defined as prostate cancer-specific mortality and/or metastatic progression, is shown (a) among men with localized prostate cancer at diagnosis in the overall cohort, (b) men of European ancestry, and (c) men of non-European ancestry. Participants were classified into low-, intermediate-, and high-risk groups using GenProb-PCSM. Age was used as the time scale, with delayed entry at prostate cancer diagnosis. Clear separation in cumulative incidence was observed across GenProb-PCSM risk groups in the overall cohort and in both ancestry groups

## References

1. Lu L, et al. Germline Genetic Risk and Prostate Cancer-Specific Mortality in a Population-Based Incident Cohort. Prostate Cancer Prostatic Dis. (2026)
2. Wei J, et al. GenProb-PCSM: A Simplified Weighted Germline Score for Prostate Cancer-Specific Mortality. Prostate (2026)

