Prostate cancer genetic risk in Africa: evaluating polygenic risk scores and germline testing

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Background
Prostate cancer (PCa) has significant ancestral disparity, with African men at greatest risk for disease and lethality over European and Asian men. However, developments in genomic PCa risk prediction and germline testing panels have been largely calibrated for men of European ancestry. Hence, polygenic risk scoring (PRS) for European men consistently outperforms African men, raising concerns over exacerbating disparities in health and precision medicine. Likewise, we demonstrated limited clinical value for current germline testing panels for men of African ancestry. While PCa PRS has been tested in men of African ancestry from the UK Biobank, these men are primarily of West African origin, who are genetically distinct to Southern and East Africans. Expanding on our previous work that only assessed PRS for aggressive disease risk, we assess PRS utility for overall PCA risk and aggressiveness in a larger cohort across South-East-West Africa. We further report potentially pathogenic/oncogenic variants identified in DNA damage repair (DDR) and PCa-related genes, highlighting key considerations for germline testing panels for African populations.

Methods
Blood-derived DNA of 378 African cases and 89 controls were whole-genome sequenced to an average 43X coverage and variant-called using a hg38 pipeline. Ancestry was classified using unsupervised ADMIXTURE analysis. For PRS, the cohort was scored using PLINK for the current 451 risk variant set. Defining aggressive disease as ISUP 4-5, or PSA ≥ 20ng/mL, logistic regression was performed using the genetic scores for PCa risk and aggressive disease. A subset of these samples (186 South African), with addition of 31 West African men, were previously interrogated for potentially pathogenic variants (PPVs) and potentially oncogenic variants (POVs). Known pathogenic variants in DDR/PCa-related genes were identified through ClinVar/InterVar. POVs were identified by removing known pathogenic/benign variants and filtering for functional prediction (SIFT, PolyPhen), and inclusion as an oncogenic driver (Cancer Genome Interpreter). Filtering for rarity and clonal haematopoiesis of indeterminate potential (CHIP, variant allele frequency <30%), we derived the candidate PPV/POVs. Finally, to prioritise genes, we used a 9 step ranking system using variant, clinical and tumour features to rank the candidate genes.

Results
Polygenic scoring showed differences in our African cohort compared to previous UK Biobank scores for men of European and African ancestry, suggesting African-specific variants need consideration in PRS design. A total of 172 PPV/POVs were identified in 78 DDR/PCa-related genes. The top-ranked candidates included *PREX2*, *POLE*, *FAT1*, *BRCA2*, *POLQ*, *LRP1B* and *ATM*, with notable DNA polymerases (*POLG*), Fanconi anaemia genes (FANC family), and DNA mismatch repair genes *MSH3* and *PMS1* outranking *MSH6* and *PMS2*.

Conclusions
These findings provide the first evaluation of common and rare variance across Southern Africa, and emphasise the need for equitable, ancestry-informed genetic risk assessment and germline testing panels for African populations.

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Conflict of Interest Disclosure Statement
The authors declare no conflicts of interest.