HEROIC Prostate Cancer Precision Health Africa1K: updates from the Genomics & Data Science Working Group

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Background: Being a male of African ancestry is a significant risk factor for prostate cancer (PCa), aggressive disease and associated death. However, not all Black men are ancestrally equal, while within Sub-Saharan Africa, PCa presentation varies between populations and regions. Representing the richest and deepest-rooting global genetic diversity, the Health Equity Research Outcomes and Improvement Consortium (HEROIC) Prostate Cancer Precision Health (PCaPH) Africa1K team are taking an Africa-and-African-inclusive and multi-disciplined approach to unravelling this disparity.
Methods: The HEROIC PCaPH Africa1K objective - to harness the power of cutting-edge multi-omic technologies and 'big-data' computational analytics, with clinicopathological and lifestyle data, in a unique 'patient-matched African-relevant' study design, to uncover the etiology of high-risk PCa and associated health disparities in African men. The target resource, 1,000 African men with advanced PCa, representing southern (South Africa, Namibia), eastern (Kenya) and western (Nigeria, African American) African ancestries. Launched in 2022, the Genomics & Data Science Working Group, led out of the University of Sydney, has initially focused on generating African-relevant pipelines for whole genome and deferential methylation interrogations.
Results: Initial studies have emphasized the need for African-specific workflows, from calling pathogenic germline variants (Zhou et al., 2025) to optimizing somatic variant detection (Jiang et al., 2025), while filtering for African-appropriate methylation probes (Craddock et al., 2025). Through pilot analyses for the first roughly 100 southern African PCa blood-tumor genomes and tumor-derived methylomes, against roughly 50 risk-matched non-African genomes and methylomes, the team have revealed that African patients present with: (1) an unmet spectrum of candidate PCa risk alleles (Soh et al., 2023) and (2) rare pathogenic mutations (Gheybi et al., 2023), including new candidate DNA damage repair and polymerase genes (Gheybi et al., 2025) and under-appreciated kilo-to-mega base derived variants (Gong et al., 2025), (3) a larger number and spectrum of cancer drivers, including an all-variant clinically-relevant molecular taxonomy, with both ancestrally-shared and African-specific representation (Jaratlerdsiri et al., 2022), (4) a bias towards driver genes impacting epigenetic regulation (Craddock et al., 2023), with (5) notable inclusion of clinically-relevant acquired structural variants (Gong et al., 2022), while (6) shortened tumor telomere lengths were associated with African-biased aggressive disease (Huang et al., 2024). Moving from the diploid genome, (7) while non-Africans were 3.1-fold more likely to present with a Y-chromosomal rare potentially deleterious germline variant, Y-chromosomal somatic copy number (CN) losses were not only more frequent for African tumors, Y-impacted CN gains appear to be African-specific (Soh et al., 2025).
Conclusion: Providing much-needed first insights into the genomic landscape of high-risk PCa in African men, through a 2023 Prostate Cancer Foundation Challenge Award the team is expanding their efforts to include further differentiation of low-risk disease with adverse outcomes commonly observed for African patients.

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