The negative impact of continued exclusion of racial groups from research on cancer genomics

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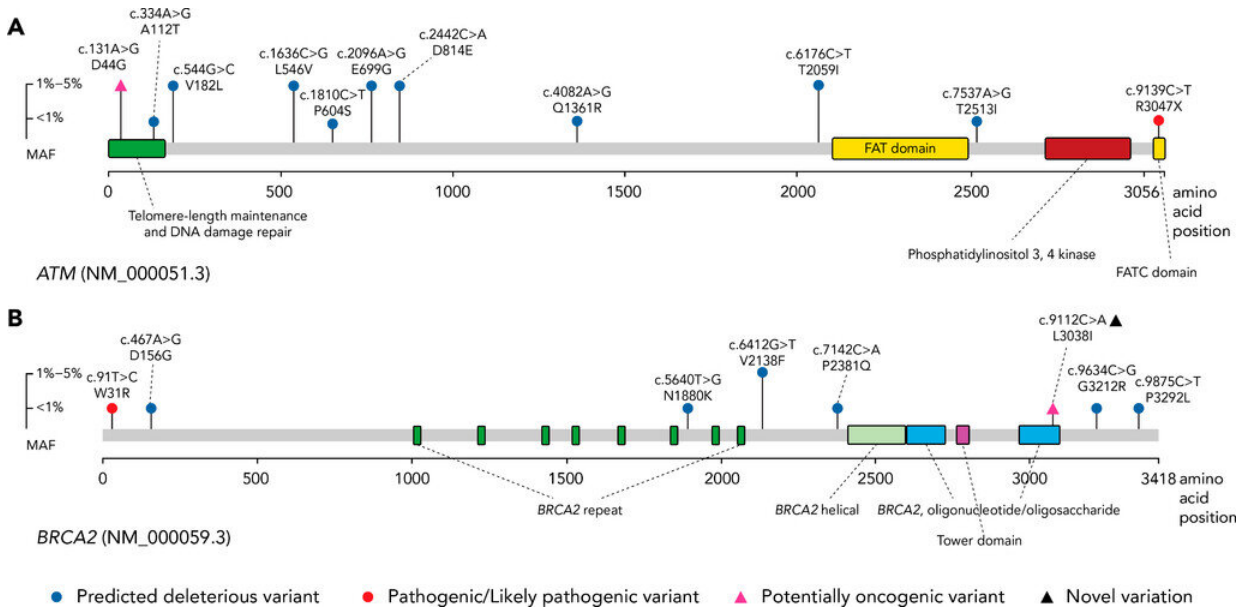

Amino acid position, MAF, and variant type, including pathogenic/likely pathogenic (ClinVar/InterVar), potentially oncogenic (CGI), predicted deleterious (SIFT/PolyPhen), splice variant, or novel, identified in 113 patients of African ancestry with PCa for the genes presenting with the highest number of potentially impactful germline variants in our study: (A) ATM and (B) BRCA2. Abbreviations: CGI, Cancer Genome Interpreter; MAF, minor allele frequency; PCa, prostate cancer; PolyPhen, Polymorphism Phenotyping v2; SIFT, Sorting Intolerant From Tolerant. Credit: *Journal of the National Comprehensive Cancer Network* (2023). DOI: 10.6004/jnccn.2022.7097

New research in the March 2023 issue of *JNCCN—Journal of the National Comprehensive Cancer Network* highlights how the lack of genomic research for people with African ancestry, particularly those from the Sub-Saharan region, is hampering efforts to reduce disparities for people with cancer. In a first-of-its-kind study, the researchers evaluated molecular genetic results for 113 Black South African men diagnosed with advanced prostate cancer to find evidence for increased and potentially unique genetic testing recommendations.

The researchers point out that, according to the GLOBOCON 2020 studies, the regions of the world most impacted by prostate cancer mortality include populations with significant African ancestry, such as the Caribbean and the regions of Sub-Saharan Africa, with mortality rates 3.4- and 2.5-fold greater, than reported for the United States, respectively. Within the United States, African American men are at 2.3- to 5-times increased risk for prostate cancer associated death than their non-African American counterparts.

"Although men of African ancestry have the highest incidence rates for aggressive prostate cancer and associated death globally, due to lack of available data, no tailored testing criteria have been established for such populations at increased risk" said lead researcher Kazzem Gheybi, MD, Ph.D., of The University of Sydney in Australia. "This study opens the door to begin to establish new criteria, providing men of African ancestry with hope that germline testing can change current disparities in clinical outcomes."

"The African diaspora is highly diverse, so I caution against regarding the most genetically diverse population in 'singular' terms," added senior researcher Vanessa M. Hayes, Ph.D., also from The University of Sydney and the University of Pretoria in South Africa. "What is required is concerted effort for inclusion that takes a grassroots approach. We need to build criteria based on population-specific knowledge. We

encourage cancer care and germline screening providers to establish a research and development arm tailored specifically for African inclusion. We need to move away from the one-size-fits-all model for prostate cancer care; African solutions should address African-relevant disparities in prostate cancer outcomes."

The study included a close examination of 21,899 single-nucleotide variants, 4,626 small insertions and deletions, and 73 structural variants across 20 genes from the 113 patients. After initially excluding variants that were known not to be cancer-causing, they found 38 mutations across 52 patients. A total of 17 pathogenic (4) and potential oncogenic (13) variants were identified. The 5.6% rate of rare cancer-causing variants in this population was significantly lower than the established rate of 11.8% for non-African patients with confirmed metastatic prostate cancer, suggesting decreased sensitivity of current gene panels for risk assessment in this patient population.

"This study highlights the poor clinical utility (30%) of the currently most-utilized germline testing panels in men of African ancestry, largely due to minimal inclusion of these groups in the development of the panels," commented Samuel L. Washington III, MD, MAS, Assistant Professor of Urology; Epidemiology & Biostatistics, University of California, San Francisco (UCSF) Helen Diller Family Comprehensive Cancer Center, who was not involved in this research.

Dr. Washington, who is also a Member of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Panel for Prostate Cancer Early Detection, continued, "This study emphasizes two crucial domains: 1) it provides further evidence of the need for greater inclusivity in genetic panel development and 2) it recognizes that disparities in outcomes for men of African ancestry can't be explained solely by the findings in 113 Black South African males.

"Although the NCCN Guidelines for Prostate Cancer Early Detection identify Black/African American identity as a risk factor, the panel notes the contributions of poor access to care, social determinants of health/social risk, and heritable genes to these observations. I look forward to further research in this area that examines how the limitations of our current tools can be improved to better reflect the populations we serve."

More information: Kazzem Gheybi et al, Evaluating Germline Testing Panels in Southern African Males With Advanced Prostate Cancer, *Journal of the National Comprehensive Cancer Network* (2023). DOI: 10.6004/jnccn.2022.7097

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