Genetic score predicts risk of lethal prostate cancer

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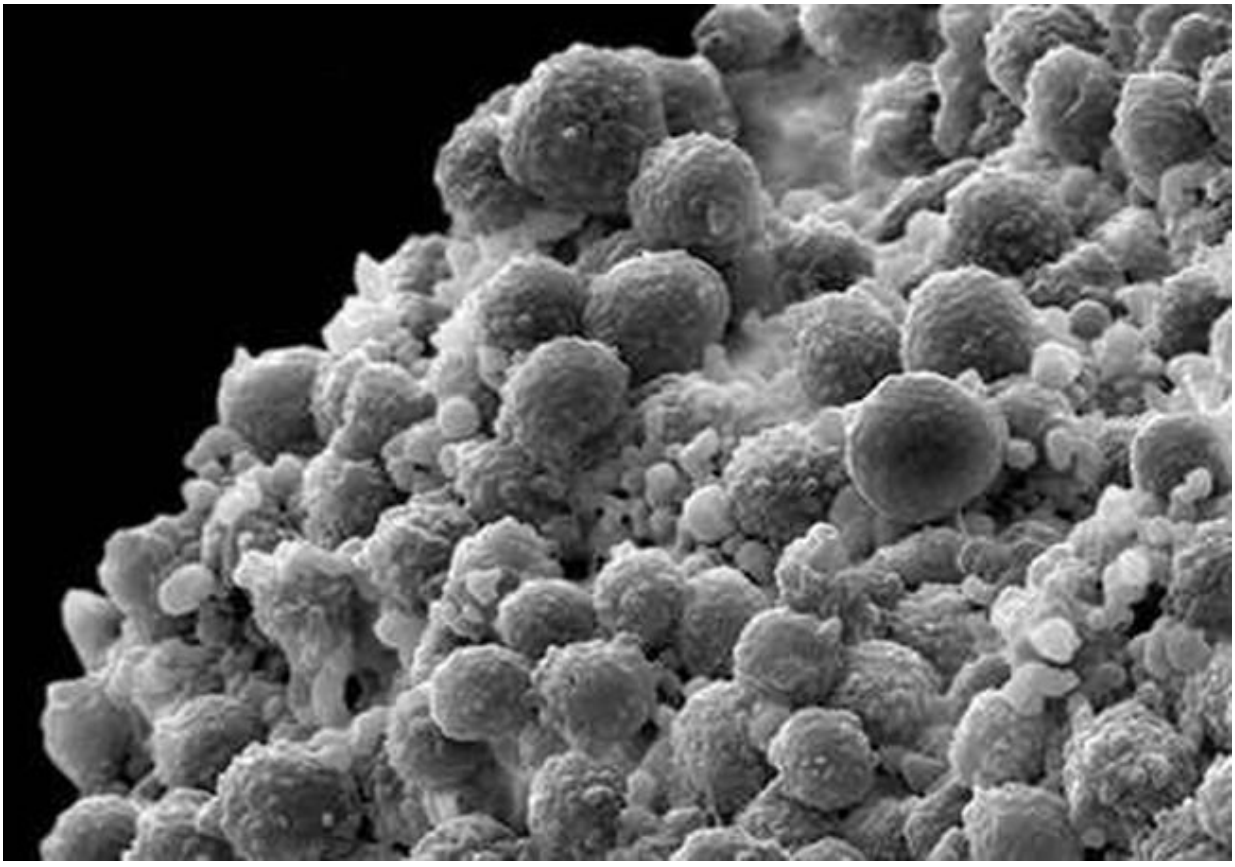

A scanning electron micrograph depicts a clump of prostate cancer cells. Credit: Cell Image Library

Tapping into the Million Veteran Program, an ongoing national research effort to learn how genes, lifestyle and military exposures affect the

health of participants, researchers at University of California San Diego School of Medicine and the VA San Diego Healthcare System, with colleagues elsewhere, report that a polygenic hazard score based on 290 genetic variants could be an effective tool for predicting genetic risk of lethal prostate cancer.

The findings are published in the October 28, 2022 issue of the *Journal of the National Cancer Institute*.

After skin cancer, prostate cancer is the most common cancer affecting men, with 268,490 new cases each year and 34,500 deaths, according to the American Cancer Society. In the United States, the lifetime risk of being diagnosed with prostate cancer is approximately 11 percent, and the lifetime risk of dying of prostate cancer roughly 2.5 percent.

"Men at highest risk of metastatic or fatal prostate cancer are potentially the most likely to benefit from screening or early detection," said Meghana S. Pagadala, Ph.D., a medical and graduate student in the Medical Scientist Training Program at the UC San Diego School of Medicine and lead author of the study.

The most common screening test for prostate cancer is the prostate-specific antigen (PSA) test, which measures blood levels of a protein. Higher levels of PSA in the blood may indicate prostate cancer, but a number of other factors can also affect PSA levels, and screening everyone comes with the potential for unnecessary biopsies and diagnosis and treatment of a low-grade cancer that does not pose a serious threat to the patient.

"Current guidelines recommend doctors discuss the advantages and disadvantages of screening with their patients. The guidelines recommend stronger consideration of screening for men with highest risk, but it is not simple for primary care doctors to estimate a given

patient's risk of dying from prostate cancer. A comprehensive, objective assessment of each patient's risk could make this much easier for doctors and patients," said senior study author Tyler M. Seibert, MD, Ph.D., assistant professor in the departments of Radiation Medicine and Applied Sciences, Radiology and Bioengineering at UC San Diego School of Medicine.

In the study, researchers analyzed 290 genetic variants known to be associated with prostate cancer risk in a diverse population of nearly 591,000 men participating in the Million Veteran Program, including a significant percentage of Black men, who are at high average risk of prostate cancer but who are often treated as a homogeneous high-risk group. Median age at last follow-up was 69 years.

"Current clinical guidelines for determining individualized risk assessment focus on race and ethnicity and family history," said Seibert. "We've demonstrated in this study, based on a very large, diverse and longitudinal cohort, that a polygenic score adds considerably more information. Patients and their doctors can have a much better idea of which individuals are at highest risk of aggressive prostate cancer."

Seibert noted that men with a high risk of prostate cancer based on the combination of race, family history and genetics may still have false-positive PSA tests or low-grade prostate cancer. Anyone undergoing prostate cancer screening should be advised of tools like prostate MRI prior to biopsy and of active surveillance if they are diagnosed with a low-grade cancer.

The new study builds upon earlier work by Seibert and colleagues, who developed and first described the polygenic hazard score for predicting age of onset of prostate cancer in 2018.

More information: Meghana S. Pagadala et al, Polygenic risk of any,

metastatic, and fatal prostate cancer in the Million Veteran Program, *JNCI: Journal of the National Cancer Institute* (2022) DOI: 10.1093/jnci/djac199. academic.oup.com/jnci/advance- … jnci/djac199/6777270