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Genetic test could identify which prostate cancers require treatment

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The level of expression of three genes associated with aging can be used to predict whether seemingly low-risk prostate cancer will remain slow-growing, according to researchers at the Herbert Irving Comprehensive Cancer Center at Columbia University Medical Center. Use of this three-gene biomarker, in conjunction with existing cancer-staging tests, could help physicians better determine which men with early prostate cancer can be safely followed with "active surveillance" and spared the risks of prostate removal or other invasive treatment. The findings were published today in the online edition of *Science Translational Medicine*.

"Most of the 200,000 prostate cancers diagnosed each year in the U.S. are slow growing and will remain so, but the three-gene biomarker could take much of the guesswork out of the diagnostic process and ensure that patients are neither overtreated nor undertreated," said study leader Cory Abate-Shen, PhD, Michael and Stella Chernow Professor of Urological Oncology at CUMC.

"The problem with existing tests is that we cannot identify the small percentage of slow-growing tumors that will eventually become aggressive and spread beyond the prostate," said coauthor Mitchell C. Benson, MD, PhD, George F. Cahill Professor of Urology and chair of urology at CUMC.

In their search for a biomarker for slow-growing prostate cancer, Dr. Abate-Shen and her colleagues, including, coauthor Michael Shen, PhD, professor of medicine and of genetics and development, focused on

genes related to aging, particularly those affected by cellular senescence, a natural phenomenon in which older cells cease to divide but remain metabolically active. Cellular senescence is known to play a critical role in tumor suppression in general and has been associated with benign prostate lesions in mouse models and in humans.

Using a technique called gene set enrichment analysis, the CUMC team, led by coauthor Andrea Califano, PhD, Clyde and Helen Wu Professor of Chemical Systems Biology and chair of systems biology, identified 19 genes that are enriched in a mouse model of prostate cancer in which the cancers are invariably indolent. They then used a decision-tree learning model, a type of computer algorithm, to identify three genes—FGFR1, PMP22, and CDKN1A—that together can accurately predict the outcome of seemingly low-risk tumors. Tumors that test negative for the biomarker are deemed aggressive.

In a blinded retrospective study, the researchers tested the prognostic accuracy of the three-gene panel on initial biopsy specimens from 43 patients who had been monitored for at least 10 years with active surveillance at CUMC. All the patients had first been diagnosed with low-risk prostate cancer (as defined by several measures, including a Gleason score of 6 or less). Of the 43 patients, 14 ultimately developed advanced prostate cancer. All 14 were correctly identified by the test.

"The bottom line is that, at least in our preliminary trial, we were able to accurately predict which patients with low-risk prostate cancer would develop advanced prostate cancer and which ones would not," said Dr. Abate-Shen.

The researchers plan to evaluate the test in a larger, prospective clinical trial, led by Dr. Benson and coauthor Sven Wenske, MD, assistant professor of urology at CUMC.

Physicians currently use several tests to diagnose prostate cancer and stage its aggressiveness. The process begins with a prostate-specific antigen (PSA) test, a digital rectal exam, or both. If these tests raise concerns, the patient is typically advised to undergo a biopsy, in which samples of prostate tissue are examined for the presence of cancer cells. If malignant cells are detected, the patient is given a Gleason score (ranging from 2 to 10), a measure of the severity of the cancer based on the cells' appearance. Patients with high Gleason scores (8 or above) are usually advised to undergo immediate treatment, while those with very low Gleason scores (5 or below) are usually advised to undergo active surveillance. "But it's not so clear what to do for patients with low (Gleason 6) or even intermediate (Gleason 7) scores," said Dr. Abate-Shen.

Men with seemingly low-risk prostate cancer currently have two basic choices. One is regular testing and monitoring, also known as active surveillance, which risks missing the window when the disease is localized and potentially curable. The other is aggressive treatment, which risks serious side effects such as urinary incontinence and impotence.

More information: The paper is titled, "A molecular signature predictive of indolent prostate cancer."

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