Study affirms value of epigenetic test for markers of prostate cancer

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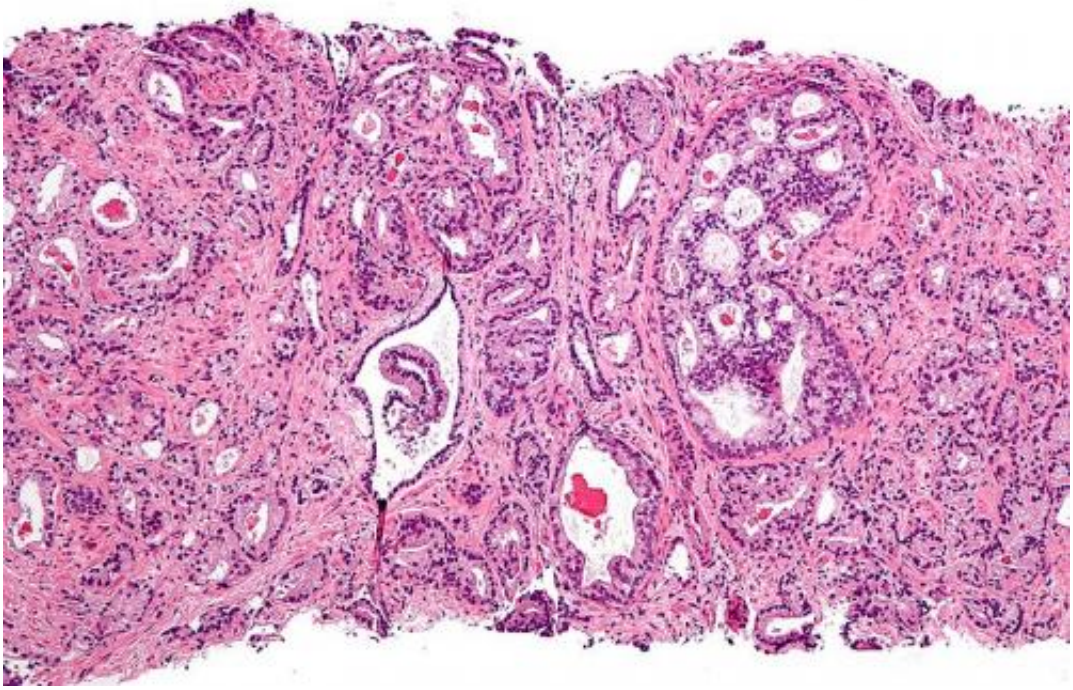

Micrograph showing prostatic acinar adenocarcinoma (the most common form of prostate cancer) Credit: Wikipedia, CC BY-SA 3.0

A multicenter team of researchers report that a commercial test designed to rule out the presence of genetic biomarkers of prostate cancer may be accurate enough to exclude the need for repeat prostate biopsies in many—if not most—men.

"Often, one biopsy is not enough to definitively rule out prostate

cancer," says study researcher Jonathan Epstein, M.D., director of the Division of Surgical Pathology and a professor of pathology, urology and oncology at the Johns Hopkins University School of Medicine. "Our research finds that by looking for the presence or absence of cancer in a different way, we may be able to offer many men peace of mind without putting them through the pain, bleeding and risk of infection that can come with a repeat biopsy."

The new research, called the Detection of Cancer Using Methylated Events in Negative Tissue (DOCUMENT) study, suggests that an initial biopsy complemented with an epigenetic diagnostic test accurately rules out the existence of cancer up to 88 percent of the time. The test, developed by MDxHealth, which paid for the study, was described online in April in The *Journal of Urology*.

The test specifically captures the presence of chemical modifications to non-nuclear DNA sequences within cells that commonly appear when prostate cancer is present. These so-called epigenetic changes, which add a methyl group to the biochemical makeup of the DNA, alter the way genes function without changing their foundational DNA sequence. The researchers analyzed tissue from biopsies from 320 men with elevated prostate-specific antigen (PSA) levels whose results were negative for prostate cancer. The men were patients at The Johns Hopkins Hospital; the University of California, Los Angeles; the Cleveland Clinic; Eastern Virginia Medical School; and Lahey Hospital & Medical Center.

The epigenetic biomarkers the test detects reflect a process called DNA hypermethylation, in which a methyl group is chemically attached to DNA—in this case, to genes called GSTP1, APC and RASSF1. These genes are known to play prominent tumor suppressive roles in key cancer-related pathways. When these genes are hypermethylated, they are commonly silenced, which can lead to a loss of this tumor-suppressing function and the emergence of cancer.

Specifically, the GSTP1 gene acts as a detoxifying agent, preventing genomic damage by carcinogens. Studies find that GSTP1 is methylated in up to 90 percent of prostate cancer cases, making it a strong indicator of the disease.

For the study, pathologists compared methylation levels between the subjects' initial tissue biopsies and later tissue samples taken from each man done within 24 months of the first biopsy. They found that average levels of APC and RASSF1 were about twice as high in the 92 subjects whose second biopsies yielded positive results, as compared to the 228 with two negative biopsies. For GSTP1, the levels were more than eight times higher in the cancerous biopsies.

"It turns out as many as 20 percent of men have prostate cancer, even if their first biopsy results are negative," says Epstein, the Rose-Lee and Keith Reinhard Professor of Urologic Pathology. Approximately 40 percent of men with a negative biopsy go on to receive a second biopsy. Many high-risk men fear sampling errors in their initial biopsy, which often leads to a high rate of follow-up procedures to merely confirm the absence of the disease.

Initial biopsies are typically performed when men receive abnormal results on PSA screenings or digital rectal exams. But an initial biopsy can sometimes miss cancer if none of the biopsy needles pass through the cancer, leading to the false-negative results.

"With prostate biopsies, there is often very little cancer, which makes it difficult to perform molecular prognostic and predictive tests," says Epstein. "The DOCUMENT study overcomes this problem, because it looks at benign tissue, not just the cancer. There is a lot of benign tissue, which is why we think it performs so well."

"Overall, if there is an absence of methylation in all three biomarkers,

there is an 88 percent likelihood you don't have cancer," Epstein says. "The test isn't 100 percent of an assurance, but it is a major step forward."

Provided by Johns Hopkins University School of Medicine