Scientists get closer to a better PSA test

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The most common screening test for prostate cancer so often returns a false positive result that it's no longer recommended for men older than 70, and it's offered as a personal choice for younger men.

But researchers think they've found a way to make the blood test for prostate-specific antigen (PSA) accurate enough to significantly reduce overdiagnosis and better predict dangerous cancers.

By calibrating PSA levels to each man's genetics, doctors could control for other factors that might cause levels to be elevated, according to researchers at Stanford Medicine, in California.

The researchers envisioned combining the regular blood-based PSA test with an additional genetic analysis that detects inherited genetic variants that can affect PSA levels.

Elevated PSA levels can be a sign of prostate cancer, but levels can also be high due to other issues like inflammation, infection, an enlarged prostate or just old age, the study authors said in background notes.

"Some men have higher PSA levels due to their genetics," senior researcher John Witte, a Stanford professor of epidemiology and population health, said in a university news release. "They don't have cancer, but the higher PSA level leads to a cascade of unnecessary medical interventions like biopsy."

By one estimate, less than one-third of men with elevated PSA levels were confirmed by a biopsy to have prostate cancer, the researchers reported. Moreover, 15% of men with normal PSA levels were later found to have prostate cancer.

But health experts are reluctant to write off the PSA test completely, given that prostate cancer rates are on the rise in the United States.

Prostate cancer rates rose by 3% a year between 2014 and 2019 after two decades of decline, and advanced prostate cancers increased by about 5% a year, the latest American Cancer Society statistics show.

The problem is that the signal delivered by current PSA screening—a man's risk of prostate cancer—is too often mixed with background noise , the researchers explained.

"To improve the signal, which is the variation in PSA levels caused by a prostate tumor, we subtract out the noise, which in this case comes from genetics," said lead researcher Linda Kachuri, an assistant professor of epidemiology and population health at Stanford.

For this study, the investigators looked at the genomes and PSA levels of nearly 96,000 men without prostate cancer to better understand the genetics behind normal variation in PSA levels. The data had been collected as part of earlier studies and included mostly men of European ancestry.

Through this analysis, the researchers estimated that 30% to 40% of the variation found in each man's PSA levels constitutes "noise," determined by genetic factors unrelated to cancer.

"Specifically, what we're trying to capture are the genetic determinants of normal PSA variation," Kachuri explained.

"This is different from our usual research deciphering the genetic basis of cancer," Witte said. "We want to remove the non-cancer-related part that's making PSA a less specific biomarker."

The researchers identified 128 specific sites in the genome that can affect a man's PSA level, and then developed a means to account for these normal genetic variations when calculating what they called a PSA polygenic score.

"A polygenic score is a quantitative way of summarizing someone's genetic predisposition for a trait in a single value," Kachuri said.

The researchers then tested their PSA polygenic score against data from a separate group of nearly 32,000 men without prostate cancer.

They found that the score could predict close to 10% of variation in PSA levels. However, it was much more effective among men of European ancestry than among men of East Asian or African ancestry.

Next, the researchers applied their score to a mixed group of men with and without prostate cancer, as confirmed by biopsy. The results showed that their PSA test could have spared roughly 30% of those men a biopsy.

The adjusted PSA levels particularly improved detection of the more aggressive forms of prostate cancer, although the benefit was noticeable only in men of European ancestry, according to the report.

"What we're really worried about are those aggressive cases, so the fact that we're able to show that genetically adjusted PSA is more predictive of aggressive disease is really promising," Kachuri said.

Unfortunately, the adjusted PSA levels also would have missed approximately 9% of positive biopsies, the findings showed.

The majority of these missed cases were slow-growing tumors, which are not as dangerous and may not even require treatment. However, the misclassifications point to room for improving the score, the study authors said.

The team next plans a larger study that will include more men from diverse populations, to better improve the accuracy of the test.

"Ideally, we want to come up with a single score that works well for everybody, across the spectrum of ancestry," Kachuri said.

Even a small improvement in screening could save lives, given that one in nine men in the United States will be diagnosed with prostate cancer and one in 40 will die from it, the researchers said.

The new study was published June 1 in Nature Medicine.

More information: Linda Kachuri et al, Genetically adjusted PSA levels for prostate cancer screening, *Nature Medicine* (2023). DOI: 10.1038/s41591-023-02277-9