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Researchers Find Keratin 17 Biomarker Shows Promise as Diagnostic Indicator for Bladder Cancer

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NEW YORK – Current practice when testing a patient for bladder cancer involves taking a urine sample and examining cells under a microscope. But that method can produce indefinite results and often misses low-grade forms of cancer, according to Kenneth Shroyer, a professor and chair of the department of pathology at Stony Brook University.

Research into a biomarker called keratin 17, or K17, could pave the way for a test that might overcome these issues and identify patients who don't need treatment.

Shroyer, along with Luisa Escobar-Hoyos, an assistant professor of therapeutic radiology at Yale School of Medicine, and a team of researchers, have studied K17 and believe it could potentially be used to diagnose all forms of bladder cancer. The researchers published their findings in the *American Journal of Clinical Pathology* earlier this month, writing that "K17 immunocytochemistry is sensitive and specific for both low-grade and high-grade urothelial carcinoma."

They added that detection of this biomarker "could be used to identify patients who are unlikely to require treatment while focusing clinical resources on the patients most likely to benefit from cystoscopy and biopsy."

While the current method for detecting bladder cancer is "relatively sensitive and specific for the most aggressive forms of bladder cancer," Shroyer said, finding low-grade cancer may be difficult. While researching keratin 17, there was a "hint that it might be expressed in both low-grade and in high-grade bladder cancer," he said.

The team confirmed it by looking at tissue specimens from cancer patients stained for K17 and found that almost all cases had expression of the protein. They then decided to test it on urine cytology samples, which showed similar performance, and developed an immunocytochemistry test for K17.

A potential issue pathologists face when doing traditional bladder cancer detection is that many microscopic appearances of low-grade cancer "may be similar to reactive processes that can occur in the bladder and are not actually cancer at all," Shroyer said.

For the study addressed in the *AJCP* paper, the team divided cases into a discovery cohort of 81 patients, where the scoring threshold for a positive result was determined, and a validation cohort of 98 patients. They found that the noninvasive test for K17 was more accurate in diagnosing bladder

cancer, with a sensitivity of 97 percent in the discovery cohort and 86 percent in the validation cohort.

The 86 percent figure is a "better reflection of what we would expect of the performance of the test in actual clinical practice," Shroyer said, as the discovery cohort was used to discover the threshold, while the validation was a test of clinical utility.

Any case where at least five malignant cells are stained for K17 on one slide is considered a positive for bladder cancer, Escobar-Hoyos said. Shroyer added that the researchers didn't find cases of cancer with less than five cells stained.

Escobar-Hoyos said another focus is measuring recurrence in patients with bladder cancer because it has a high recurrence rate. It is also able to screen for hematuria, or blood in the urine, which is a sign of recurrence, she said.

The URO17 test has a turnaround time of about 24 hours and takes only a few minutes for a pathologist to diagnose once the sample is on a slide under a microscope, Shroyer said. For both the traditional method of studying morphology and the K17 test, the slide is stained on an instrument and sent to a cytotechnologist to identify any abnormalities that are present.

It is then sent to the cytopathologist, who makes the final diagnosis and formulates a pathology report, which is added to the laboratory's electronic medical record, Shroyer said.

Some of the sites that have used the test have cut out the cytotechnologist, but he said his team's study didn't remove that step. The test can also give confidence to a cytopathologist that low-grade cancers aren't being missed, Escobar-Hoyos said.

The turnaround time for both methods is about the same, but that's "clinically not important," Shroyer said. The main benefit is that it's more accurate, helping determine patients who would benefit from biopsies and identifying patients who don't have cancer, he added. It's also easier for a pathologist to score K17 compared to morphology alone. The K17 "result is black and white, whereas [in morphology] we're trying to interpret different shades of gray," he said.

Eventually, the team hopes to have a machine score the test and provide a result so a trained cytopathologist wouldn't necessarily be needed, Escobar-Hoyos said. The team is collaborating with the biomedical informatics department at Stony Brook to develop this technology, she said.

While a final review would likely be done by a pathologist, the initial positive or negative decision would be made by the machine, Shroyer said. The team is planning to initiate studies to test the ability of digital imaging and automated instruments for this purpose within the next year and could have a digital solution in the next few years, Shroyer said.

According to Escobar-Hoyos, the machine could help save hours, although it would take time to train the machine to score the slides. Right now, the test is "really good where it is," she said. "Having it automated would just be the cherry on top."

Nikhil Vasdev, consultant urological surgeon and associate medical director for cancer in the department of urology at Lister Hospital in the UK, has also studied K17 and the URO17 test and said the "uniqueness of keratin 17 … is that if someone has cancer, it'll pick it up." He said the

URO17 test had 100 percent sensitivity, with nearly 93 percent specificity, in the study he led that was published last year in *BJUI Compass*.

One issue his research has found is "a few false positives," although two people in the study he ran were thought to have false positives but developed bladder cancer a year later, he said.

Using K17 to determine if a patient has bladder cancer can prevent people coming to the hospital unnecessarily if they have a negative result, he said. Because the COVID-19 pandemic has led many patients to wait on follow-up care, a noninvasive test like this could improve delayed diagnostics and ensure patients receive the treatment they need, he said.

Tom Jayram, director of the Advanced Therapeutics Center at Nashville, Tennessee-based Urology Associates, has used the test and said it's "quite valuable in the initial triage of patients with hematuria" and "carries quite a higher sensitivity than traditional urinary cytology and detects low-grade urothelial carcinoma very well."

"A negative K17 test in my opinion is a very good indicator that no further testing for bladder cancer is needed," he added.

He also noted the test's value in monitoring patients with previously treated bladder cancer "as high positive K17 results can indicate cancer has returned and prompt further evaluation." He said that more data is needed for the recurrent setting to show how best to use the marker, but it has performed "quite well" in the diagnostic setting.

However, Jayram also mentioned issues with false positives, particularly in patients with prior prostate or bladder cancer, pelvic radiation, or infection.

Commercialization plans

Nam Kim, CEO and chief technology officer of KDx Diagnostics, also participated in the research, and his company has exclusively licensed the biomarker and the URO17 test. He and Shroyer have been collaborating for about 25 years, and Kim said the data was "so striking" for K17 in bladder cancer that he knew it needed to be commercialized.

The test received Breakthrough Device Designation from the US Food and Drug Administration last year and is currently undergoing a multicenter clinical trial for FDA marketing clearance. It has been available as a laboratory-developed test since 2019 and is offered at AcuPath, a Long Island, New York-based laboratory that serves customers across the US.

Kim noted that Los Gatos, California-based KDx is also in discussions with expanding the test to a bigger national reference laboratory, although he declined to disclose the lab.

It has also received CE-IVD marking and is available in Europe and the United Kingdom. Kim said the company is trying to expand the test to Japan, but COVID-19 "put a damper on everything" because many regulatory processes were put on hold for a year.

The test is reimbursable under the generic immunohistochemistry CPT code, and claims for the test have gotten "almost no rejection" from payors. However, the firm plans to build up its publications and is doing a medical economic study so it can petition for its own specific CPT code, Kim said.

It is also working with Cardiff University in Wales and CellPath to develop a home collection kit for the test's urine sample, Kim said. In the US, the firm is beta testing the urine kit and expects it to be available on a limited basis by the end of the year. The key to making the kit work is developing a preservative for the sample, Kim said.

The company also has the same goal as Shroyer and Escobar-Hoyos of making the test "more pathology independent," and getting it automated, Kim said. Outside of the US, there is a "severe lack of pathologists," and automating the test could make it more accessible for laboratories in those regions, he added.

Keratin 17 was originally used as a marker for cervical cancer and has applications in pancreatic, head and neck, breast, and endometrial cancers. However, the expression of the protein is different than in bladder cancer, making it more of a prognostic marker to guide therapy rather than a diagnostic marker, Kim said, noting that KDx is pursuing applications for K17 in other cancers.

The technology is "basically the same" as with bladder cancer, but the difference would be in sample type, according to Kim.

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