Simple noninvasive test may lead to breakthrough in early diagnosis of bladder cancer

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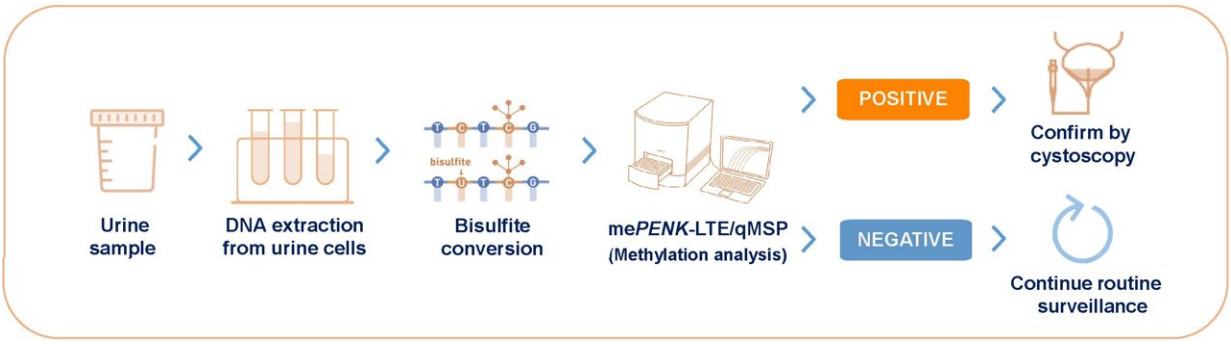

A schematic overview of the sample processing and mePENK-LTE/qMSP assay for detecting bladder cancer. Fresh voided urine samples were collected into tubes containing preservative buffer. Total DNA was extracted from the urine sediments and underwent bisulfite conversion. Subsequently, linear target enrichment (LTE) and quantitative methylation-specific PCR (qMSP) were conducted to determine the level of PENK methylation associated with bladder cancer. A positive result indicates a higher probability of bladder cancer, suggesting further cystoscopy is needed to confirm the diagnosis. Conversely, a negative result indicates a lower or no risk of bladder cancer, thereby allowing for the avoidance or postponement of cystoscopy. Credit: Genomictree, Inc.

Bladder cancer has a five-year survival rate of over 80% when detected early, but this rate declines significantly as the disease progresses to advanced stages. In a novel study in *The Journal of Molecular*

Diagnostics, investigators report on a promising new diagnostic tool that may pave the way for an important breakthrough in early diagnosis of bladder cancer in patients with blood in their urine (hematuria), reducing the number of potentially unnecessary invasive cystoscopies and alleviating the economic burden of the disease.

One of the most common symptoms of bladder cancer is hematuria, which accounts for up to 20% of all urological visits. Hematuria is seen in approximately 85% of bladder cancer patients. However, hematuria is prevalent among adults and may have other causes. From 5-20% of hematuria cases are diagnosed with bladder cancer.

Lead investigators Sungwhan An, Ph.D., CEO and Scientific Director, Genomictree, Inc., Daejeon, South Korea, and Ju Hyun Shin, MD, Department of Urology, Chungnam National University College of Medicine, Daejeon, South Korea, explain, "Diagnosing bladder cancer at an early stage is critical and not only can increase patient survival rates but can also contribute to reducing health care costs."

"Current guidelines recommend cystoscopy and imaging examinations for almost all patients presenting with hematuria for initial diagnosis of bladder cancer, but it is invasive, inconvenient, economically burdensome for patients, and frequently fails to detect early-stage bladder cancer. There is therefore an urgent need for a sensitive and precise technique to diagnose early bladder cancer effectively among patients with hematuria."

Investigators studied a novel biomarker called aberrant PENK methylation (mePENK), which has shown a high clinical correlation with bladder cancer in previous studies. The first of two independent studies focused on developing a highly sensitive methylation test for mePENK using urine DNA and evaluating its effectiveness in diagnosing bladder cancer in patients within the hematuria population.

The cutoff value for the mePENK test was initially determined in a case-control study involving 175 bladder cancer patients and 143 non-malignant hematuria patients. The test exhibited a sensitivity of 86.9% and a specificity of 91.6% in distinguishing bladder cancer from non-malignant hematuria cases.

A subsequent independent prospective clinical performance study comprising 366 hematuria patients scheduled for cystoscopy compared the mePENK test results with the cystoscopy findings and histological analysis as the reference standards. The overall sensitivity of the test in detecting 38 cases of bladder cancer at all stages was 84.2%, while the specificity reached 95.7%. Notably, the test demonstrated a sensitivity of 92.3% in detecting high-grade and advanced-stage bladder cancer.

Dr. Shin notes, "Although the FDA (U.S.) has approved several urine biomarker–based products, these methods have not been effectively utilized for early bladder cancer diagnosis. There are some in vitro molecular diagnostic techniques that measure genetic and epigenetic biomarkers for bladder cancer that are undergoing clinical trials, but they have yet to provide sufficient clinical evidence for the initial diagnosis of primary bladder cancer."

Dr. An adds, "In this study, we used a test based on a single biomarker, mePENK, to detect primary bladder cancer in hematuria patients, and compared its clinical performance with tests that combine multiple biomarkers. Surprisingly, our findings revealed that the mePENK test was equal to or even superior to these multiple biomarker tests."

"Furthermore, the noninvasive nature of using a urine sample and the simplified test procedure offer advantages such as a shorter turnaround time for sample processing and efficient and accurate analysis of results."

Sungwhan An concludes, "The present study showcases a breakthrough in diagnosing bladder cancer through a simple and effective diagnostic test that eliminates the need for unnecessary cystoscopy procedures."

"The results demonstrate high sensitivity and accuracy in detecting bladder cancer. Using void urine as a sample offers significant advantages, ensuring easy accessibility to diagnostic opportunities for patients. The test has the potential to significantly reduce bladder cancer–related deaths and medical expenses. To implement the test in clinical practice larger-scale prospective clinical trials are needed, and we are actively pursuing that goal."

Bladder cancer is the sixth most common cancer in the world. Bladder cancer has a five-year survival rate of over 80% when detected early, but this rate significantly declines as it progresses to advanced stages, necessitating bladder removal and having a high risk of recurrence. As a result, bladder cancer ranks among the most expensive cancers to treat and manage.

More information: Tae Jeong Oh et al, Evaluation of Sensitive Urine DNA-Based PENK Methylation Test for Detecting Bladder Cancer in Patients with Hematuria, *The Journal of Molecular Diagnostics* (2023). DOI: 10.1016/j.jmoldx.2023.05.003

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