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European Association of Urology



## Letter to the Editor

### Reply to Chao Song's Letter to the Editor re: Florus C. de Jong, Iris G. Iffé, Angélique C. van der Made, et al. A Genomic Urine Assay for Surveillance of Patients with Bladder Cancer Treated with Radiotherapy. *Eur Urol Open Sci* 2024;62:131–9

We would like to thank Dr. Song for the interest and valuable comments regarding our manuscript [1]. Our study demonstrated that a noninvasive urine test—based on a simple multiplex polymerase chain reaction analysis on DNA isolated from voided cells detected in urine—can be used to monitor bladder cancer (BC) in patients treated with bladder-sparing radiotherapy. Detection of somatic mutations in urinary circulating tumor DNA (ctDNA) derived from supernatant is technically more complex, but the idea is similar [2]. Currently, urine diagnostics for monitoring patients with muscle-invasive BC (MIBC) are understudied, probably because of fear that high-risk recurring disease might be missed, leading to progression and poor clinical outcomes. Therefore, cystoscopy and computed tomography scans should remain part of the study design for future randomized controlled interventional trials. For example, as in non-muscle-invasive BC, we strongly believe that cystoscopy can be alternated with our test to safely reduce the number of cystoscopies, thereby improving patient comfort and quality of life while decreasing costs [3]. In addition, urine cytology can be omitted as it is often inconclusive because of radiation-induced cellular degeneration and/or the presence of inflammatory cells.

Dr. Song writes a compelling argument for use of our test in another clinical scenario, that is, to predict treatment response and minimal residual disease (MRD) in patients with MIBC undergoing neoadjuvant immunotherapy (or chemotherapy, or any other neoadjuvant treatment). Other groups showed that ctDNA is excellent at predicting oncological outcomes. Several ongoing trials are investigating if ctDNA can drive therapeutic decisions, such as adjuvant immunotherapy (eg, the TOMBOLA and MODERN trials) [4]. In the neoadjuvant setting, it may be worth investigating whether undetectable ctDNA can help in preselecting patients for definitive or delayed bladder-sparing treatment [5].

As for our test, several limitations must be investigated when detecting MRD. First, an important caveat is the potential for false-negative results in cases with low tumor burden because of a low number of shed cancer cells. Second, our test uses commonly altered BC-related alterations, but some mutations can also be present in normal-appear-

ing urothelium that are thought to originate from field cancerization effects and may lead to false-positive test results [6]. Finally, specificity close to 100% would be required to determine whether radical cystectomy can be withheld. Adjustments to our test might be necessary to reach such a level of accuracy. Still, despite these caveats, the simplicity of the test and the low cost make it easily accessible worldwide, even in regions without the (technical) capabilities needed to investigate ctDNA. Hence, we strongly encourage Dr. Song and others to explore urine tests in this patient setting.

**Conflicts of interest:** The authors have nothing to disclose.

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