



## Letter to the Editor

**Re: F. Johannes P. van Valenberg, Andrew M. Hiar, Ellen Wallace, et al. Prospective Validation of an mRNA-based Urine Test for Surveillance of Patients with Bladder Cancer. Eur Urol. 2019; 75,5: 853-860**

We read with great interest the recent publication by van Valenberg and colleagues [1]. The authors analyzed the diagnostic accuracy of a noninvasive urine test, Xpert Bladder Cancer Monitor (Xpert), for follow-up of patients previously diagnosed with non-muscle-invasive bladder cancer (NMIBC) in a prospective multicenter study. The study showed that Xpert had overall sensitivity (SN) of 74% and a negative predictive value (NPV) of 93%, which were superior to the corresponding values for cytology and UroVysion. The authors conclude that Xpert is a promising tool for surveillance of NMIBC patients. We congratulate the authors on their exciting work. However, we feel some issues need to be clarified to understand this study better.

From the study, Xpert with high SN (74%), NPV (93%), and specificity (SP; 80%) seems promising as an “ideal” noninvasive urine test [1]. A recent study on Xpert for follow-up of NMIBC patients by D’Elia et al. [2] revealed similar NPV (83%) and SP (77%), but much lower overall SN (46.2%) compared to the values reported by van Valenberg et al, although the SN results for high-grade (HG) tumors (85.7% [2] vs 83% [1]) were comparable. In fact, there were more low-grade (LG) tumors (LG 45, HG 7) in the study by D’Elia et al than in the van Valenberg cohort (LG 19, HG 24). Moreover, SN of 40% for LG tumors in the D’Elia study [2] was much lower than that in the van Valenberg study (63%) [1]. Considering the discrepancy between the studies for LG tumors and the small number of patients with LG tumors in the van Valenberg cohort, the performance of Xpert for LG tumors remains questionable. In addition to Xpert, the Cxbladder Monitor test (Cxbladder) is a noninvasive urine test for surveillance of bladder cancer that tests mRNA of five different genes also included in Xpert. Cxbladder showed overall SN of 91% and NPV of 96% in a study that included 1036 urine samples from 803 patients, and the SN for LG tumors was also relatively high (84%) [3]. Combination or modification of Xpert and Cxbladder may further optimize noninvasive urine testing.

The authors claim that bacillus Calmette-Guérin (BCG) treatment within 90 d before an Xpert test did not influence

the results. However, with only nine patients experiencing recurrence among the 49 treated with BCG before enrollment [1], larger samples are required for further validation. While some NIMBC patients receive intravesical chemotherapy rather than BCG during oncological follow-up, the influence of intravesical chemotherapy on Xpert test results should also be evaluated before its application in the clinic. Hematuria usually occurs in NIMBC patients undergoing bladder cancer surveillance, and it remains unknown whether hematuria can interfere with the Xpert test.

Relatively low Xpert positive predictive values of 44% [1] and 36.9% [2] were observed in both studies, suggesting that only a small proportion of positive Xpert results were also positive on cystoscopy. Long-term follow-up is required for patients with false positive results, as small papillary tumors and flat carcinoma in situ lesions are often missed by standard cystoscopy. It will be exciting if Xpert can detect tumors missed by standard cystoscopy. In addition, it has been reported that some of the genes tested in Xpert are overexpressed in upper tract urothelial carcinoma (UTUC) [4]. Thus, patients with false positive results might have UTUC, but this possibility was not ruled out in the study.

Ostrowski et al. [5] described their experience with a single-use digital cystoscope in a cohort of 51 patients, who reported an average pain score of 0.98 out of 10 during the procedure. Patients also stated that they suffered less or significantly less pain compared to rigid cystoscopy in 95.0% and compared to flexible cystoscopy in 87.5% of cases. The urologists in the study also reported that the single-use cystoscopes worked well. Thus, single-use disposable cystoscopes might be an excellent alternative to regular cystoscopes for surveillance of NIMBC patients.

To summarize, the accuracy of Xpert, especially for LG tumors, remains to be evaluated in further high-quality studies. Patients might have less pain and more choices if the performance of the noninvasive urine Xpert test and single-use cystoscopes is validated in the future.

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

## References

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