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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;75:853–60

We read with great interest the article by van Valenberg and colleagues [1]. In the first prospective multicenter study, the authors analyzed the diagnostic accuracy of the Xpert Bladder Cancer Monitor test in the surveillance of 239 patients previously diagnosed with non–muscle-invasive bladder cancer (NMIBC). In summary, the authors confirmed sensitivity (SN) of 75% and negative predictive value (NPV) of 93% overall, and SN of 83% and NPV of 98% for high-grade (HG) tumors [1]. However, it is well known that cytology already has high sensitivity for HG tumors, but is limited by its low sensitivity for low-grade (LG) tumors [2].

Thus, the "ideal" urinary-based marker with high sensitivity even for LG tumors but without a reduction in specificity is still needed to replace cystoscopy in surveillance. Concerning LG tumors, van Valenberg et al demonstrated that the Xpert test was significantly more sensitive than cytology or UroVysion (63% vs 5.3% vs 21%) [1]. Moreover, previous intravesical bacillus Calmette-Guérin or chemotherapy instillations (64% of the patients) did not negatively influence diagnostic accuracy [1], in contrast to other urinary markers such as the BTA stat test [3]. Therefore, the authors conclude that Xpert may be the first step forward in modifying follow-up schedules because of its better diagnostic performance and similar specificity compared to cytology (80% vs 90%).

The findings by van Valenberg et al are in line with results from our previous single-center prospective study presenting the first Xpert data for 140 patients with a history of NMIBC undergoing surveillance. We reported overall SN of 84% for Xpert, 9% for voided urine cytology, and 33% for barbotage cytology, with similar specificity compared to cytology. Among LG tumors, Xpert achieved higher SN (77%) compared with voided urine cytology (3%) and barbotage cytology (13%) [4]. The specificity in our study

(91%) was higher than in the study by van Valenberg et al (80%). This may be explained by the exclusion of patients with hematuria or nephrolithiasis and a lower rate of previous instillation therapies in our study population (42.2%) compared to the trial by van Valenberg et al (64%).

Nevertheless, some open topics remain that should be discussed. (1) Compared to barbotage cytology (70%) [4], the positive predictive value (PPV) of Xpert for voided urine at 44% [1] and 36.9% [5] was relatively low, implying that only a few positive results were "truly positive" on cystoscopy. (2) Despite negative cystoscopy, is a "positive" Xpert result predictive of recurrence over time? To answer this question, further trials with long-term follow-up data for patients with "false-positive" results would be very interesting. (3) As a positive test for voided urine may indicate an urothelial tumor anywhere in the urinary tract, how did the authors exclude urothelial cell carcinoma in the upper urinary tract?

To summarize, we think that the excellent accuracy of Xpert must be confirmed in further external validation studies, and there is a need for the test to become more cost-effective in the future for widespread use.

Conflicts of interest: The authors have nothing to disclose.

References

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February 14, 2019