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LETTER TO EDITOR

# Towards the future of upper tract urothelial carcinoma surveillance: lessons learnt from bladder cancer urinary biomarkers

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Dear Editor,

Recently, three papers have been published to summarize and highlight the role of urinary biomarkers in the detection of non-muscle invasive bladder cancer (NMIBC), analyzing 177 studies [1–3]. The clinical utility of urinary biomarkers may range from screening and diagnosis to surveillance and monitoring of topical therapy response [1]. Several urinary biomarkers for NMIBC are approved by the Food and Drug Administration for diagnosis and surveillance (NMP22 and BTA tests), prediction of intravesical BCG response (ImmunoCyt®) or both (UroVysion®) [2]. Despite this, urinary biomarkers are not routinely integrated in the international guidelines and, although a randomized controlled trial is ongoing (UroFollow trial; FF-FB0241), are not indicated to replace cystoscopy [1].

This is due to several factors: (1) the majority of the studies are not designed to apply the biomarker in specific scenarios; (2) a single biomarker binary model (yes/no) is not truly discrete; (3) the phases of research (preclinical, assay development and validation, external validation, and post-approval reports) are not respected and (4) cost-effectiveness is usually not evaluated [4]. However, new panel DNA-based (AssureMDx, Bladder EpiCheck) and RNA-based tests (Xpert Bladder, Cxbladder) were developed, all characterized by high sensitivity (68–97%)/negative predictive value (NPV; 93–99.6%) and potentially fit for NMIBC surveillance [2, 3, 5]. These new biomarkers seem promising, since they could lead to mutational surveillance in an individualized process of care.

As for NMIBC, the heterogenous (epi)genetic landscape that characterizes upper tract urothelial carcinoma (UTUC) reduces the utility of a single biomarker. Moreover, urinary cytology cannot be considered an accurate tool for UTUC detection [6]. Therefore, biomarker panels may represent the future to decrease control ureteroscopies and, thus, morbidity during long-term endoscopic management of UTUC. To date, their clinical application has been explored in few studies.

GDF15/TMEFF2/VIM promoter methylation in voided urines of 22 UTUC patients versus 20 controls showed sensitivity, specificity, NPV, positive predictive value of 91%, 100%, 91%, and 100%, respectively [7].

The combination of GDF15/TMEFF2/VIM/CDH1/RASSF1A/HSPA2 methylation in voided urine samples of 98 UTUC and 113 controls resulted more accurate (AUC 0.836; NPV 81%) than FISH (AUC 0.81; NPV 55%) and urinary cytology (AUC 0.56; NPV 36%) [8].

In the effort to provide a commercially available urinary biomarker characterized by high sensitivity/NPV for urothelial cancer, we conducted an exploratory study on Bladder EpiCheck in UTUC. Bladder EpiCheck, which analyzes methylation status of 15 genes, demonstrated high sensitivity (91.7%) and NPV (99.3%) for high-risk NMIBC [5]. We prospectively collected voided and selective urine samples from six patients and submitted to ureteroscopy for radiological suspicion of UTUC. Bladder EpiCheck was positive in 3/3 high-grade UTUC (100%) in both selective and voided urine and in 1/2 (50%) of low-grade UTUC and correctly identified the healthy patient (100%). These preliminary

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results showed the feasibility of Bladder EpiCheck to be used in UTUC. Therefore, a prospective single-center non-randomized trial is ongoing. We strongly believe that the lessons learnt from NMIBC urinary biomarker studies will help the scientific community to properly select an "easier, better, faster, cheaper" [9] urinary biomarker for UTUC surveillance.

**Author contributions** Gallioli: project development, data collection, and manuscript writing/editing. Boissier: data analysis and manuscript editing. Territo: data collection and management. Breda: project development and manuscript editing.

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## Compliance with ethical standards

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** After ethical committee approval, all patients enrolled in our study signed an informed consent.

**Conflict of interest** All the authors declare that they have no potential conflicts of interest.

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