Reply to ‘It May be Time to Abandon Urine Tests for Bladder Cancer’

“…for whom the bell tolls, It tolls for thee.”
- John Donne

The article, “It May be Time to Abandon Urine Tests for Bladder Cancer”1 reinforces what is widely known within urology: that current urine-based assays for the diagnosis of bladder cancer are subpar. Briefly, the FDA has approved 4 urine-based assays for bladder cancer detection (UroVysion for initial evaluation and tumor surveillance, ImmunoCyt for tumor surveillance, BTA stat for initial evaluation and tumor surveillance, NMP-22 for initial evaluation and tumor surveillance). We have shown that BTA stat is a surrogate for hematuria2 and NMP-22 identifies states of cellular proliferation,3 and thus it is no wonder one can have positive BTA stat or NMP-22 test results in the face of a benign condition. The lack of robustness is also well documented with ImmunoCyt and UroVysion.4 Voided urinary cytology (VUC), the gold standard for noninvasive monitoring, lacks sensitivity, especially in low-grade and low-stage disease. Although VUC is recommended in the American Urological Association (AUA) guidelines for the evaluation of bladder cancer, it is used in <10% of these evaluations.5 The use of these urine-based assays continues to decline each year. Accordingly, current urine tests for bladder cancer are “dead.”

As is evident in most cancers, single biomarkers have inadequate predictive power, and thus the concept that the presence or absence of a single molecular biomarker will aid diagnostic or prognostic evaluation has not proved to be the case. This makes sense when one analyzes the complex interactions between various molecules within a single pathway, the cross-talk between molecular pathways, the redundancy of some pathways, and the oligoclonality of many tumors. Thus, we previously proposed a paradigm shift from single biomarker research to a more global assessment of bladder cancer looking for molecular signatures associated with the disease. Other disease sites have embraced this notion and now have assays in clinical use (eg, Oncotype Dx Colon, MammoPrint, and Genomic Prostate Score).

Although Fantony and Inman1 reinforce these points, little information is given about promising new leads. Several groups are on the precipice of potentially bringing such a multiplex assay to the clinic. For example, in a large multicenter study of 789 subjects, Ribal et al6 recently reported that their 5-gene expression signature consisting of ANXA10, DAB2, HYAL2, SPOCD1, and MAP4K1 possessed a sensitivity and specificity of 81% and 91%, respectively. At the 2016 AUA meeting in San Diego, in a large cohort of 803 subjects, Lotan et al7 reported a 4-gene-expression signature consisting of CDC2, MDK, IGFBP5, and HOXA13, which possessed a sensitivity and negative predictive value of 93% and 97%, respectively. Furthermore, our group previously reported on a multiplex panel of protein biomarkers consisting of ANG, APOE, A1AT, CA9, IL8, MMP9, MMP10, PAI-1, SDC1, and VEGF8. After review of pooled data from 999 subjects, meta-analysis showed that the combination of 10 biomarkers possessed a higher log odds ratio (3.61; 95% CI, 2.90–4.32) than any single biomarker (H.F. and C.J.R., unpublished data; 2017). Subsequently, we launched a multicenter prospective trial to test the assay in patients with hematuria (gross and microscopic, n=1,600) and those undergoing surveillance for bladder cancer (n=400). Thus, several groups may be within 5 years of having a new validated multiplex assay available for effective cancer risk
assessment, early detection, and early diagnosis of bladder cancer, ushering in a new era in bladder cancer diagnosis.

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References

Authors’ Reply to Letter to Editor: “Reply to ‘It May be Time to Abandon Urine Tests for Bladder Cancer’”

Furuya and Rosser suggest that the problem with current urine tests is that they are not yet good enough. They argue that with further optimization and development and by combining multiple molecular tests, urine tests for bladder cancer will become dramatically more useful.

Although we agree that urine tests for bladder cancer will probably become more refined and their diagnostic performance (ie, sensitivity and specificity) will improve to a degree, there are more fundamental problems with urine tests for bladder cancer than the tests themselves. In fact, we suggest that the problem lies less with the specific tests and more with the medical decision-making scenario to which they are applied. For example, we recently reported a study of 4,023 cytology-cystoscopy pairs and 1,696 UroVysion fluorescence in situ hybridization (FISH)–cystoscopy pairs that showed very significant and clinically relevant differences in urine test performance by patient characteristics.1 Both urine cytology and UroVysion FISH had an increase in sensitivity and a decrease in specificity among older patients, male patients, and former smokers. FISH performed much better in patients with a prior diagnosis of bladder cancer than in those being evaluated for hematuria.1 It should be noted that in all of these groups, the performance of these tests was poor. This type of testing problem is known as spectrum bias, and seems to be a particular problem for urine-based bladder cancer tests. It illustrates that great consideration is required regarding how the tests perform in different patient populations, because this appears to substantially affect test performance.

When dealing with a test for cancer, false-positive and false-negative results can lead to serious consequences, and in the case of urine tests for bladder cancer, this actually happens quite frequently. Test manufacturers often claim that a positive urine
test is “accurate” even when the gold standard cystoscopy is negative. They claim that this false-positive test will eventually become a true-positive if you follow the patient over time with more cystoscopies, a phenomenon that has been termed the anticipatory positive test. That more cystoscopies will eventually detect more bladder cancer is, of course, guaranteed, because bladder cancer tends to recur over time due to the biology of the disease, and regardless of the urine test result. The issue of false-positive versus anticipatory positive urine tests was carefully examined for FISH and cytology in a recent publication. The take-home message is that although a positive urine test is associated with an increased probability of developing a future bladder cancer, it is not a guarantee of a future cancer. Many of these initially false-positive urine tests remain falsely positive, even when credited up to a year of follow-up time in which the tumor they are purportedly detecting is allowed to occur.

One of the main goals of an office-based urine test should be to replace the need for more invasive screening/surveillance, such as a cystoscopy. The penchant for bladder cancer to recur necessitates frequent procedural follow-up, which is costly and has psychosocial ramifications for patients. To date, no urine test has been developed that has come close to reaching the goal of substituting for cystoscopy, which then begs the question: why are we spending precious healthcare money on urine tests that don’t change how bladder cancer surveillance occurs?

Should a combination urine assay be developed that uses several biomarkers, each of which has their own sensitivity/specificity for diagnosing bladder cancer, its overall accuracy will still be subject to the influence of spectrum bias in the population being tested. To illustrate this point, we will use the following scenario: a patient with a history of low-grade, noninvasive bladder cancer is in the office for routine follow-up 1 year after his transurethral resection of bladder tumor. A new urine test that uses 2 biomarkers is going to be used, and the results will dictate whether he needs an office cystoscopy. Biomarker A has excellent sensitivity for detecting recurrent bladder cancer but marginal specificity, whereas biomarker B has marginal sensitivity but excellent specificity for detecting recurrent bladder cancer. This test should prove useful in that biomarker A would act as a screening test, whereas biomarker B would be confirmatory. However, the uncertainty that is introduced by patient-related factors (eg, demographics, disease state, exposure history) and tumor-related factors creates a scenario in which the interpretation of a positive or negative result could be difficult. A Bayesian approach could be used to interpret the results of this combined assay, and the overall test performance will be affected by how each individual biomarker performs in that particular patient’s clinical context.

This scenario is demonstrated in a multicenter study of 2 novel biomarkers being added to urine cytology and FISH in an attempt to improve their clinical performance. Therefore, given the uncertainty of urine testing, most clinicians would likely just go ahead with office cystoscopy.

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References