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In Honor of Claus G. Roehrborn, M.D.

UT Southwestern Medical Center

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To Medical Directors Novitas

Re: Cxbladder Triage Test

It is my privilege to provide a letter regarding the potential clinical utility of Cxbladder Triage in evaluation of patients with hematuria. I am Dr. Yair Lotan, Professor of Urology and Chief of Urologic Oncology at UT Southwestern Medical Center. My clinical and academic career has been dedicated to advancing the care of patients with bladder cancer. I have authored over 650 peer-reviewed publications, several book chapters, and hold patents related to bladder cancer detection. I am a member of the AUA guidelines panel for hematuria. I am chair of the American Urologic Association Clinical Trail Collective and prior chair of the AUA core curriculum. I serve as a reviewer for leading medical journals and have been a principal investigator and co-investigator on multiple NIH-funded and investigator-initiated clinical studies, including several large collaborative biomarker studies such as CxBladder (STRATA, CREDIBLE, LOBSTER). I am also involved in a R01 funded trial called "Replace Cysto" (NCT05796375) which is a multisite randomized phase 2 trial including 240 participants with low-grade intermediate-risk non-muscle-invasive bladder cancer, in which participants will be randomized 1:1:1 to one of two urine marker-based approaches alternating a urine marker test (Xpert Bladder Cancer Monitor or Bladder EpiCheck) with cystoscopy or to frequent scheduled cystoscopy.

My professional service includes active participation in AUA, SUO, IBCG, and BCAN, and I have been honored with several awards for contributions to the bladder cancer field. Clinically, I have managed thousands of bladder cancer patients across my career and contributed to the development of guidelines that define the standard of care for bladder cancer diagnosis and treatment.

Through this work, I have seen firsthand the significant burden that bladder cancer places on patients and their families. I also have identified the frequent delayed diagnosis of patients due to inadequate evaluation of patients with hematuria. The goal of the updated AUA/SUFU hematuria guidelines was to improve risk stratification of patients with hematuria to prioritize evaluation of high risk patients and reduce the burden of evaluation on patients with lower risk for urologic malignancies (PMID: 40013563). One aspect of improving proper evaluation of hematuria patients and improving compliance among primary care physicians is to integrate the use of well-studied urine-based tumor markers into the diagnostic algorithm for microhematuria. The AUA guidelines state that “In appropriately counseled intermediate-risk patients who want to avoid cystoscopy and accept the risk of forgoing direct visual inspection of the bladder urothelium, clinicians may offer urine cytology or validated urine-based tumor markers to facilitate the decision regarding utility of cystoscopy.” There is a significant amount of literature demonstrating that only a small percentage of patients with microhematuria undergo comprehensive evaluation for their condition.(PMID: 23312369, PMID: 23153858,

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PMID: 20564400) Furthermore, delays in diagnosis are considered one of the reasons for the reduced survival among bladder cancer patients. One reason that primary care physicians (PCPs) do not refer patients is their concern about the need for an invasive procedure such as cystoscopy. This requires a referral to urology since PCPs cannot perform this procedure. Urine-based tumor markers such as Cxbladder Triage offer multiple advantages. They can be ordered by PCPs and do not require referral to urology. If the test is negative then there is a 99% negative predictive value for bladder cancer so very rare cancers will be missed and most will be low grade. If the test is positive then the likelihood of cancer is higher and the population evaluated by urologists will be enriched by patients at higher risk.

I was a participant on the STRATA study which was a Multicenter Prospective Randomized Controlled Trial Comparing Cxbladder Triage to Cystoscopy in Patients with Microhematuria (PMID: 38700731). Compared to cystoscopy, Cxbladder Triage had 90% sensitivity, 56% specificity, and 99% negative predictive value for UC. The arm that used Cxbladder Triage had significantly fewer cystoscopy procedures and detected all the high grade cancer patients. This study led to a strength of evidence of "A" among markers that can be used in evaluation of intermediate risk patients with hematuria.

If the test is readily available then there will be several immediate consequences. First, I will discuss this marker in all eligible patients who want to avoid cystoscopy. Secondly, I will discuss the use of the marker to our PCPs at UT Southwestern to consider prior to referral for eligible patients who want to avoid cystoscopy.

There are many examples of patients who likely could benefit from urine marker testing. For example, a 70-year-old woman with no risk factors for bladder cancer, no history of smoking and 3 red blood cells per high powered field is considered intermediate risk according to the AUA guidelines. Her risk for bladder cancer with a negative Cxbladder triage would be less than 3 per 1000 and she could just be monitored rather than undergo cystoscopy.

I expect the availability of urine marker testing will improve evaluation of hematuria patients overall as it will lead PCPs to consider evaluation in more patients and in a more timely manner.

Sincerely

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