THE JOURNAL of UROLOGY®
www.auajournals.org/journal/juro



# What Is the Future of Cystoscopy for Detecting Urothelial Carcinoma?

Asymptomatic microscopic hematuria (AMH) is a common finding that leads to many urology referrals. Occasionally, patients with AMH harbor urothelial carcinoma of bladder (UCB). The 2020 AUA AMH guidelines recommend risk-stratifying patients based on their risk of UCB and offering cystoscopy to intermediate- and high-risk patients. However, the vast majority of AMH patients do not have UCB, and even the highest-risk group has a prevalence of $< 10\%$.[1] In addition, most AMH patients are classified as intermediate- and high-risk and should be evaluated for UCB, but the majority are not referred to urology at all.[1,2] Therefore, our system for evaluating patients with hematuria has 2 weaknesses: (1) urologists perform a large number of negative invasive tests, and (2) urologists miss the opportunity to evaluate many patients with hematuria who are at risk for UCB. Is there a better way to rule out UCB in patients with hematuria than urology referral and flexible cystoscopy?

Imaging alone is inadequate, and urine cytology has a poor sensitivity for UCB in the hematuria population. However, this space is fertile ground for a novel noninvasive biomarker. In theory, a high-sensitivity test that can accurately identify patients with UCB could help avoid the unnecessary evaluation of patients who do not have the disease and facilitate urology referrals for those who may.

CxTriage (CxT) is one such biomarker that combines clinical data (sex, age, smoking history, history of gross hematuria) with 5 mRNAs (MDK, CDK1, IGFBP5, HOXA13, CXCR2) in a voided urine sample to estimate the risk of UCB for patients with gross and microscopic hematuria. In a 2015 study, Kavalieris et al assessed 627 hematuria patients evaluated by urology.[3] Most of these patients (94%) had gross hematuria, and 72 UCBs were detected. CxT had a 95% sensitivity for UCB and tested negative in 40% of patients. This study was limited by a low number of AMH patients, among whom no cancers were detected. In another cohort of 478 hematuria patients having a urologic evaluation (70% with gross hematuria), 44 UCBs were detected including 3 in patients with microscopic hematuria.[4] In this study, CxT had a sensitivity of 95.5% and negative predictive value (NPV) of 98.6% with about a third of patients testing negative. For the microscopic hematuria group only, the sensitivity was 100%. The rare, missed cancers among test-negative patients were low grade and noninvasive, suggesting the risk of a false-negative CxT was low.

When used as a triage test by primary care providers in a cohort of 884 hematuria patients, CxT combined with imaging reduced hematuria referrals to urology by 40% while maintaining a 98% sensitivity and 99% NPV for detecting UCB.[5] The UCBs that were missed by CxT were all noninvasive. While CxT is not perfect, given the rare, missed cancers (which are uncommonly dangerous) and the 10% nondiagnostic rate, it allowed primary providers to capture nearly all UCBs in their hematuria patients and appropriately refer these patients to urology.

Recently, Lotan et al published a prospective randomized trial to determine if CxT could decrease cystoscopy among lower-risk AMH patients.[6] The patients randomized to CxT tested negative approximately 88% of the time, the majority of whom chose to defer cystoscopy. The authors observed a nearly 60% reduction in cystoscopy between patients who had CxT and those who did not. Among lower-risk patients who did have a cystoscopy, only one tumor was identified (1.7% prevalence). The risk of a false-negative test in CxT-negative patients who did not have a cystoscopy was presumed to be very low based on prior research.

Other studies suggest that CxT performs well in the higher-risk AMH population[7] and may lead to cost savings by decreasing cystoscopy use. Furthermore, a newer version of CxT with 2 additional gene mutations (FGFR and TERT) demonstrated improved performance to CxT alone, indicating these markers are likely to continue to improve.

There are other novel genomic urinary biomarkers to detect UCB among patients with hematuria. One assay incorporates methylation of OTX1, ONECUT2, and TWIST1 along with DNA mutations of FGFR3, TERT, and Harvey HRAS.[8] Among 1005 hematuria patients who had a urologic evaluation, 112 UCBs were found (including 14



https://doi.org/10.1097/JU.0000000000004071
Vol. 212, 399-400, September 2024
Printed in U.S.A.

UCBs among 381 AMH patients). The assay had a 98% sensitivity and would decrease cystoscopy use by over 50%, with the only missed cancer among test-negative patients being a low-grade noninvasive UCB. Among AMH patients specifically, the assay performed well with a 93% sensitivity and 100% NPV. Another assay uses 60 somatic mutations in urinary cell-free DNA to identify UCB, and in patients with hematuria it had a 98% sensitivity and 99% NPV.[9]

The findings from the Lotan study[6] suggest that physicians trusted the CxT results and uncommonly recommended a cystoscopy with a negative test, and that the concept of reducing unnecessary cystoscopies in the hematuria population is an important and achievable goal. As the sensitivities of these biomarkers approach or surpass that of white light flexible cystoscopy, patients are likely to preferentially accept them in place of cystoscopy.[10]

Urologists are already comfortable using biomarkers to avoid invasive testing, which we routinely do for patients with an elevated PSA to determine the need for a prostate biopsy. These tests include blood-based (PHI, 4K, free PSA), urine-based (Intelliscore, SelectMDx, MiPS, MiR), and tissue-based biomarkers (ConfirmDx), as well as imaging (MRI). Depending on the test, these biomarkers will identify 20% to 30% of patients as low-risk, who may safely defer a prostate biopsy with a very low chance of missing a clinically significant cancer. As evidenced by the ProScreen and STHLM3-MRI studies, these biomarkers help patients avoid prostate biopsies without compromising detection rates of significant disease and decrease the detection of indolent cancer.

Although these novel biomarker studies raise important questions about evaluating patients at risk for UCB, these tests have the potential to improve the management of our patients with suspected UCB who would otherwise require an invasive procedure for diagnosis. This also holds true for nonmuscle-invasive bladder cancer patients who require cystoscopic surveillance, for whom several novel biomarkers, including but not limited to CxMonitor, UroAmp, and Uromonitor, have demonstrated high sensitivities for UCB and may allow patients to defer cystoscopy.

The need for cystoscopy to diagnose UCB is unlikely to change anytime soon even if triage tests are used, as all marker-positive patients still require cystoscopy. However, we must acknowledge that reducing the number of negative cystoscopies for patients at risk for UCB is a desirable goal. And if these biomarkers are employed in the first-line setting, it may ultimately improve appropriate hematuria referrals to urology and avoid the referral delays that some hematuria patients face. Given the landscape of novel urinary biomarkers in the hematuria space, with early studies reporting sensitivities well over 90%, we are challenged to understand these tests, educate patients about them, and determine how to best incorporate them into our practices.

**Christopher B. Anderson**[1,2]
[1]*Assistant Editor, The Journal of Urology®*

[2]*Department of Urology*
*Columbia University Irving Medical Center*
*New York, New York*

Submitted May 15, 2024; accepted May 19, 2024; published June 7, 2024

## REFERENCES

1. Woldu SL, Ng CK, Loo RK, et al. Evaluation of the new American Urological Association guidelines risk classification for hematuria. *J Urol*. 2021;205(5):1387-1393. doi:10.1097/JU.0000000000001550
2. Matulewicz RS, Demzik AL, DeLancey JO, Popescu O, Makarov DV, Meeks JJ. Disparities in the diagnostic evaluation of microhematuria and implications for the detection of urologic malignancy. *Urol Oncol*. 2019;37(5):300.e1-300.e7. doi:10.1016/j.urolonc.2019.01.007
3. Kavalieris L, O'Sullivan PJ, Suttie JM, et al. A segregation index combining phenotypic (clinical characteristics) and genotypic (gene expression) biomarkers from a urine sample to triage out patients presenting with hematuria who have a low probability of urothelial carcinoma. *BMC Urol*. 2015;15:23. doi:10.1186/s12894-015-0018-5
4. Davidson PJ, McGeoch G, Shand B. Inclusion of a molecular marker of bladder cancer in a clinical pathway for investigation of haematuria may reduce the need for cystoscopy. *N Z Med J*. 2019;132(1497):55-64.
5. Davidson PJ, McGeoch G, Shand B. Assessment of a clinical pathway for investigation of haematuria that reduces the need for cystoscopy. *N Z Med J*. 2020;133(1527):71-82.
6. Lotan Y, Daneshmand S, Shore N, et al. A multicenter prospective randomized controlled trial comparing Cxbladder triage to cystoscopy in patients with microhematuria. The safe testing of risk for asymptomatic microhematuria trial. *J Urol*. Published online May 3, 2024. doi:10.1097/JU.0000000000003991
7. de Jong JJ, Pijpers OM, van Kessel KEM, et al. A urine-based genomic assay improves risk stratification for patients with high-risk hematuria stratified according to the American Urological Association guidelines. *Eur Urol Oncol*. 2023;6(2):183-189. doi:10.1016/j.euo.2022.08.002
8. van Kessel KEM, de Jong JJ, Ziel-van der Made ACJ, et al. A urine based genomic assay to triage patients with hematuria for cystoscopy. *J Urol*. 2020;204(1):50-57. doi:10.1097/JU.0000000000000786
9. Salari K, Sundi D, Lee JJ, et al. Development and multicenter case-control validation of urinary comprehensive genomic profiling for urothelial carcinoma diagnosis, surveillance, and risk-prediction. *Clin Cancer Res*. 2023;29(18):3668-3680. doi:10.1158/1078-0432.CCR-23-0570
10. Bullock N, Mubarak M, Morris C, et al. Perception of urinary biomarker tests among patients referred with suspected urological malignancy. *BJUI Compass*. 2023;4(4):446-454. doi:10.1002/bco2.234