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A Multicenter Prospective Randomized Controlled Trial Comparing Cxbladder Triage to Cystoscopy in Patients With Microhematuria: The Safe Testing of Risk for Asymptomatic Microhematuria Trial

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Study Need and Importance: Hematuria evaluation is recommended for most patients with microhematuria but compliance with recommendations is low, potentially delaying or missing diagnosis of bladder cancer. We hypothesized that a urinary biomarker with a high sensitivity/negative predictive value, Cxbladder Triage (CxbT), could triage patients who need evaluation by identifying those at high risk and reducing evaluation in low-risk patients with negative marker.

What We Found: Patients included in the study (Figure) were classified according to our criteria into lower risk (LR; 3-29 red blood cells/high-power field and smoking < 10 pack-years) and not low-risk patients (> 29 red blood cells/high-power field and/or smoking > 10 pack-years). LR patients were randomized into marker-based and standard of care (SOC) arms. Of 390 eligible patients who enrolled into the study, 135 were LR randomized to CxbT-informed decision or SOC. In the LR arm, cystoscopy was performed in 67% of SOC and 27% in the marker group (relative risk 0.41, 95% CI 0.27-0.61) resulting in a 59% decrease. Compared to cystoscopy, CxbT had 90% sensitivity, 56% specificity, and 99% negative predictive value for urothelial cancer.

Limitations: Limitations included inability to follow-up the entire cohort of patients in LR group, impacting the ability to assess the long-term effects of the decision. Additionally, as the study was designed prior to 2020, our risk stratification did not align with the current 2020 AUA microhematuria guideline. Indeed, many of our LR patients would be intermediate or even high risk (based on age alone) in the current guidelines.

Interpretation for Patient Care: In this prospective randomized controlled trial, use of CxbT in patients with LR hematuria resulted in a 59% relative reduction of cystoscopy use. This clinical utility of CxbT can reduce the burden of unnecessary cystoscopies and thus improve overall patient care.

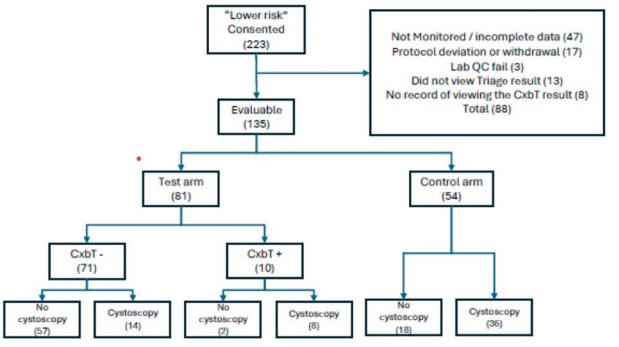

Figure. Diagram for lower-risk patients used in clinical utility analysis. CxbT indicates Cxbladder Triage; QC, quality control.

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A Multicenter Prospective Randomized Controlled Trial Comparing Cxbladder Triage to Cystoscopy in Patients With Microhematuria: The Safe Testing of Risk for Asymptomatic Microhematuria Trial

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Purpose: AUA guidelines for patients with microhematuria (≥3 red blood cells [RBC]/high-power field [hpf]) include cystoscopy for most over age 40 due to risk of urothelial cancer (UC). Cxbladder Triage (CxbT) is a urinary genomic test with UC negative predictive value of 99%. In this prospective randomized controlled trial, we compared cystoscopy use in a standard of care (SOC) arm vs a marker-based approach.

Materials and Methods: All patients with hematuria provided urine for a CxbT. Those categorized as lower risk (LR), defined as 3 to 29 RBC/hpf and minimal smoking history (<10 pack-years) were randomized between the test group

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Ethics Statement: This study received Institutional Review Board approval (IRB No. STU2019-1020). All human subjects provided written informed consent with guarantees of confidentiality.

Author Contributions:

Conception and design: Lotan, Lough, Daneshmand.
Data analysis and interpretation: Lotan, Daneshmand, Shore, Black, Scarpato, Patel, Lough, Shoskes, Raman.
Data acquisition: Lotan, Daneshmand, Shore, Black, Scarpato, Patel, Raman.
Drafting the manuscript: Lotan, Shoskes.
Critical revision of the manuscript for scientific and factual content: Lotan, Daneshmand, Shore, Scarpato, Patel, Shoskes, Raman.
Supervision: Lotan, Lough.

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provided with the CxbT result vs the SOC control group. Negative CxbT patients were offered omission of cystoscopy with surveillance. "Not lower risk" (NLR) patients (>30 RBC/hpf or >10 pack-year smoking history) had a CxbT but otherwise SOC. Patient decision and outcomes were recorded.

Results: Of 390 eligible patients, 255 were NLR and 135 were LR randomized to CxbT informed decision or SOC. The median age was 62 years (range 18-94) and 54% were male. Overall, 63% of CxbT tests were negative. For NLR patients, 82% had cystoscopy. In the LR control group, cystoscopy was performed in 67% of SOC and 27% in the test group (relative risk 0.41 [95% CI 0.27-0.61]). Compared to cystoscopy, CxbT had 90% sensitivity, 56% specificity, and 99% negative predictive value for UC.

Conclusions: In this prospective randomized controlled trial, use of CxbT in patients with LR hematuria resulted in 59% reduction of cystoscopy use. This clinical utility of CxbT can reduce the burden of unnecessary cystoscopies.

Key Words: hematuria, controlled clinical trials, randomized, genomics

Urothelial carcinoma (UC) is one of the most lethal cancers urologists treat and timely diagnosis prior to muscle invasion or metastasis improves outcomes. Because microscopic hematuria may be the first presentation of UC, the mainstay of urologic practice has been mandatory cystoscopy, even though at most 2% to 5% of patients with microhematuria have UC.[1] While evaluation of hematuria occupies a significant portion of urologic evaluation, the vast majority of adults with microhematuria do not, in fact, undergo adequate evaluation.[2-4] As such, there is a potential missed opportunity for early diagnosis. The AUA microhematuria guideline[1] directs providers regarding evaluation of patients with hematuria using a risk-based approach whereby low-risk patients may be offered the option of surveillance rather than immediate cystoscopy.[1] Nonetheless, UC is found in about 0.8% of AUA low-risk patients,[5] resulting in a heavy burden of potentially unnecessary negative cystoscopies.

A urinary biomarker with high sensitivity/negative predictive value (NPV) could help to safely reduce the burden of unnecessary cystoscopies in this population and potentially enrich those evaluated with patients who have cancer. Cxbladder Triage (CxbT) is a biomarker that combines the mRNA expression of 5 genes with 4 clinical questions to produce a score that classifies patients as low risk for UC or not low risk, with a published sensitivity of 95.1% and NPV of 98.5%.[6,7] The goal of this study was to evaluate the impact of an up-front CxbT result on the decision to proceed with cystoscopy in lower-risk patients referred for microhematuria. The hypothesis was that in a prospective randomized trial, knowledge of the CxbT result would reduce the number of cystoscopies done in lower-risk hematuria patients.

MATERIALS AND METHODS

Design

The STRATA: Safe Testing of Risk for Asymptomatic Microhematuria trial compared standard-of-care (SOC) evaluation for microhematuria in which patients were offered cystoscopy and imaging as compared to a marker-based strategy where lower-risk patients were offered a marker along with imaging and higher-risk patients were recommended cystoscopy and imaging.

In this multicenter prospective study involving 12 sites, patients > 18 years of age referred for evaluation of microhematuria per AUA guidelines[1] were offered participation and signed an Institutional Review Board–approved consent. Exclusion criteria included a prior history of urologic malignancy or pelvic radiotherapy.

Patients were stratified into lower risk (LR) and not lower risk (NLR) categories. To be classified as LR, patients had to have a ≤ 10 pack-year smoking history, no current gross hematuria, and urine microscopy showing 3 to 29 red blood cells (RBCs) per high-power field (hpf). As the trial was developed prior to the AUA 2020 guidelines, the categorization was based on number of RBCs per hpf on urinalysis and smoking exposure which differ from current guideline stratification. Those who didn't fulfill all these criteria were classified in the NLR category. All patients provided an initial urine sample for CxbT. As seen in the study schema (Figure 1), patients in the NLR category group were not provided the result of their CxbT test and proceeded with SOC evaluation per the site's normal practice. Patients in the LR category group were randomized 2:1 into those whose physicians received the CxbT result prior to deciding on cystoscopy (test group) and those who were not provided with the result (control group).

The primary objective was to evaluate the increase in utility of using CxbT to guide hematuria evaluation without compromising detection of UC, defined by the reduction in cystoscopy procedures. A secondary objective was to confirm the performance metrics of the test by calculating sensitivity, specificity, NPV, and test negative rate in patients who did have cystoscopy.

Procedures

The CxbT assay was performed as previously described at Pacific Edge Diagnostics NZ (Dunedin, New Zealand), a Clinical Laboratory Improvement Amendments–approved laboratory. Briefly, quantitative reverse transcription polymerase chain reaction was used to measure mRNA expression of 5 genotypic biomarkers (MDK, CDK1, IGFBP5, HOXA13, and CXCR2).[6] Combined with clinical questions on sex, age, smoking history, and visible hematuria, the

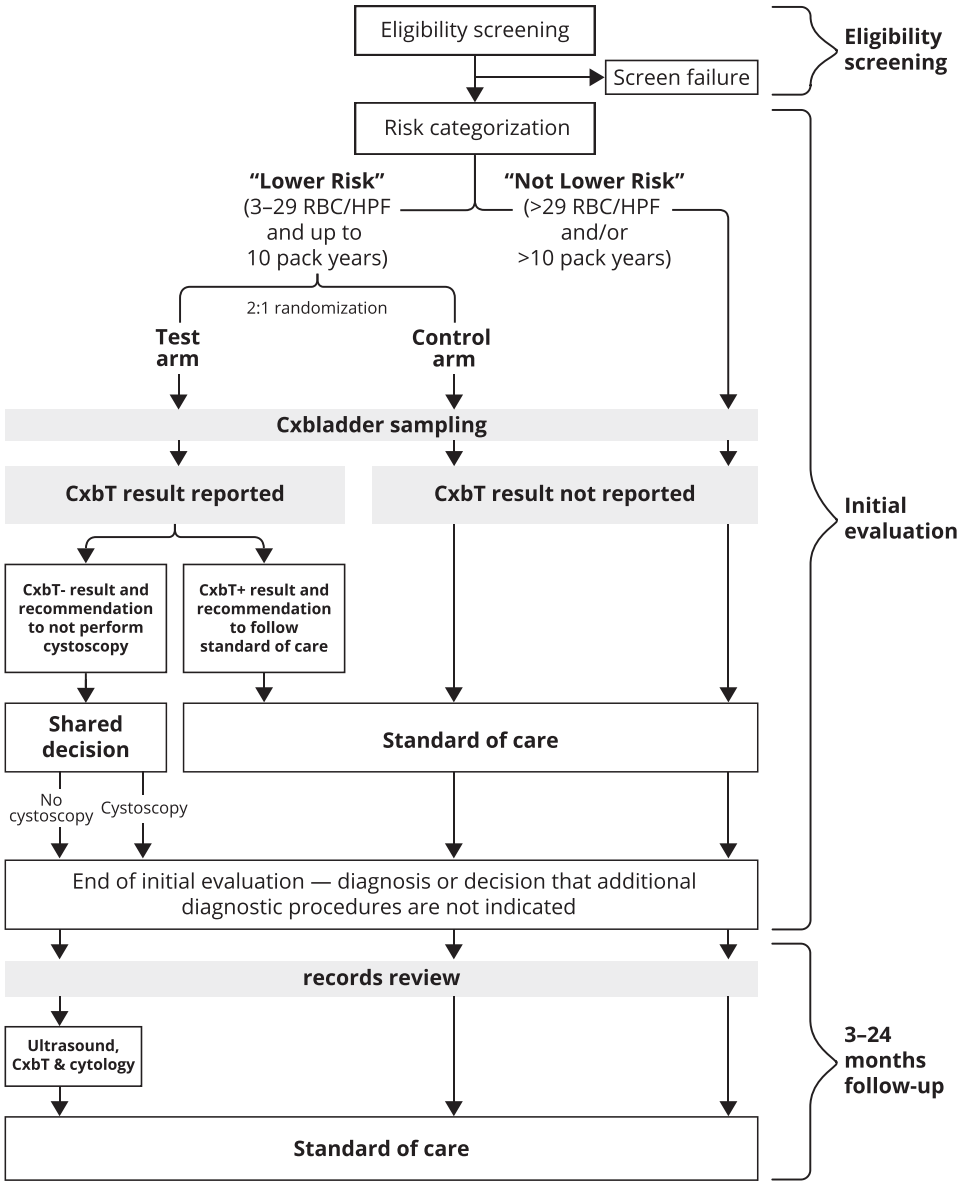

Figure 1. Study schema. CxbT indicates Cxbladder Triage; HPF, high-power field; RBC, red blood cells.

algorithm produces a score from 1 to 10. A score below 4 is classified as low probability of UC with a sensitivity of 95.1% and NPV of 98.5%. The test result was only reported prior to the decision for cystoscopy to those patients with LR randomized to the test group. For those patients with a positive CxbT, their clinician was provided with the result of the Cxbladder Detect assay, which is only based on the 5 biomarkers and doesn't include clinical questions. Cxbladder Detect has a slightly lower NPV compared with CxbT but a higher positive predictive value of 68%.[8] Patients in all groups who chose cystoscopy had conventional flexible white light cystoscopy per SOC. For any lesions identified, pathology was recorded from any subsequent transurethral resection.

Follow-Up

Patients who were not diagnosed with UC had a records review at least 3 months after their visit up to 24 months. Patients in the LR category group who were CxbT negative and did not have cystoscopy were offered bladder ultrasound, urinalysis, urinary cytology, and repeat CxbT.

Monitoring and Data Inclusion

Following independent monitoring of the data collected, there were 2 different thresholds for including patients in the analysis for calculating the primary endpoint (clinical utility) vs the secondary endpoint (clinical validity). To be included in the calculation of CxbT performance characteristics for clinical validity (Figure 2, A), they required accurate risk classification, a CxbT result, and documentation of the cystoscopy outcome (270 patients). To calculate clinical utility (Figure 2, B), LR patients randomized to the test arm had to have a valid CxbT result with documentation that the result was available and reviewed prior to the decision to proceed with cystoscopy (135 patients total). Therefore, the patient totals in each group vary according to the analysis reported.

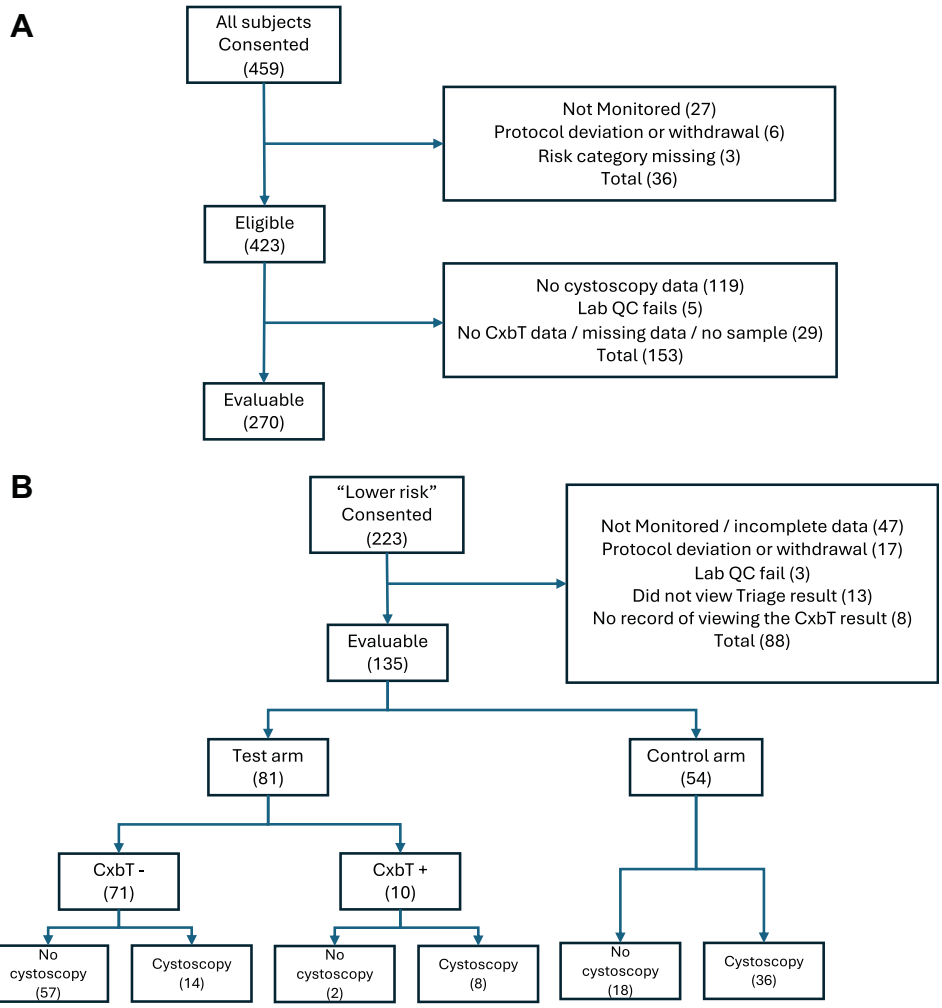

Figure 2. CONSORT diagrams. A, diagram for all patients used in performance calculations for Cxbladder Triage. B, diagram for lower-risk patients used in clinical utility analysis. CxbT indicates Cxbladder Triage; QC, quality control.

Statistical Analysis

The sample size of approximately 180 LR subjects was calculated to provide 90% power to detect a reduction in cystoscopy rates of at least 15%-points by using CxbT with an assumed cystoscopy rate in the control group of 77%. Descriptive statistics were calculated for all demographic variables. We derived estimates and confidence intervals for the absolute and relative reduction in cystoscopy rates, comparing the groups. Confidence intervals for the absolute change are based on the test of equal proportions (prop.test in R). Confidence intervals for the difference in the relative risk are based on the formula for the standard error of the log relative risk ratio.[9] The difference between the LR test and LR control groups was considered statistically significant if the confidence interval did not include the value 0 (absolute rate) or 1 (relative risk). For those subjects where both the CxbT result and the cystoscopy result (confirmed by pathology) were known, we calculated the sensitivity, specificity, NPV, positive predictive value, and their binomial exact confidence intervals.

All confidence intervals are 95%. Analysis was done in R, version 4.2.[10]

RESULTS

Overall, 538 patients were consented and 390 patients completed the protocol. The demographic information is summarized in Table 1 for the group as a whole and stratified by clinical group. Age ranged from 18 to 94 years (median 62) and 53.7% were male. The predominant racial groups included White/European at 67.5%, African American at 9.7%, and Asian at 8.9%.

There were 255 NLR category patients and 209 (82%) proceeded with cystoscopy. In this group, there were 22 tumors found (10.5%) including 12 stage Ta (5 high grade), 8 stage T1, and 1 stage T2b. There was no carcinoma in situ.

There were 135 LR category patients with 54 randomized to the control group (CxbT result not provided to doctor or patient) and 81 to the test group (result provided prior to cystoscopy decision). In the test group, the CxbT negative rate was 71/81 (87.7%) as opposed to the overall test negative rate of 63%. In this test-negative group 14 out

Table 1. *Demographics*

	Overall		LRC		LRT		NLR	
No.	538		54		81		255	
Age, mean (SD), y	60.1	(14.7)	57.1	(14.5)	55.6	(14.3)	63.4	(14.0)
Gender, No. (%)								
Female	247	(45.9)	32	(59.3)	46	(56.8)	95	(37.3)
Male	289	(53.7)	22	(40.7)	35	(43.2)	159	(62.4)
Unknown	2	(0.4)	0	(0.0)	0	(0.0)	1	(0.4)
Race, No. (%)								
African American	52	(9.7)	4	(7.4)	7	(8.6)	22	(8.6)
Asian	48	(8.9)	6	(11.1)	10	(12.3)	23	(9.0)
White/European	363	(67.5)	37	(68.5)	51	(63.0)	190	(74.5)
Other	73	(13.6)	7	(13.0)	13	(16.0)	19	(7.5)
Unknown	2	(0.4)	0	(0.0)	0	(0.0)	1	(0.4)
Nonsmoker (10 pack-y or less), No. (%)	412	(76.6)	54	(100)	80	(98.8)	153	(60.0)
At-risk occupation (present), No. (%)	132	(24.5)	5	(9.3)	19	(23.5)	70	(27.5)

Abbreviations: LRC, low-risk control; LRT, low-risk test; NLR, not lower risk; SD, standard deviation.

of 71 (19.7%) chose to have a cystoscopy, and in the test-positive group 8/10 (80%) chose to have a cystoscopy. For the primary study endpoint, the proportion of LR patients having cystoscopy in the control arm was 67% as compared to 27% in the test arm, a reduction of 59%. As seen in Table 2, the absolute reduction in cystoscopy was statistically significant comparing LR test patients with LR control patients, LR test patients between those with a negative or positive CxbT result, and overall between the LR and NLR groups. The change in cystoscopy rates between groups is represented in Figure 3.

In the LR category group as a whole 58/135 (43%) had cystoscopy and 1 tumor was found (1.7%), which was a multifocal high-grade stage T1, and in this patient the CxbT result was positive.

For the 22 tumors found in total, imaging results are available for 21 patients. In 14 (67%) there was a finding in the bladder suspicious for tumor by ultrasound[7] and/or CT scan[11] and 1 patient with unilateral hydronephrosis.

There were 270 patients total who had both a cystoscopy done and a CxbT result. Table 3 shows the CxbT results for these patients as well as subgroup analysis by risk. For the patients who had cystoscopy, the calculated sensitivity of CxbT for UC was 90% (95% CI 70%-99%), the specificity was 56% (49%-56%), the NPV was 99% (95%-100%), and the positive predictive value was 15% (9%-22%). For high-grade disease, sensitivity was 100% (78%-100%), specificity 56% (49%-62%), NPV 100% (97%-100%), and positive predictive value 12% (7%-19%). For the subset of LR patients who had both the CxbT and cystoscopy (75 patients), sensitivity was 100% (3%-100%), specificity 77% (66%-86%), NPV 100% (94%-100%), and positive predictive value 5.6% (0.1%-27.3%).

Overall, 367 patients in all cohorts had follow-up data and the median time between the initial consultation and records review was 372 days. For the 57 LR patients who were CxbT negative and chose not to have cystoscopy, some follow-up data were available in 48 and a follow-up CxbT was done in 29. There was one such patient who 13 months later had a CxbT that was then positive, and cystoscopy showed a single high-grade Ta tumor. In the NLR cohort, there was 1 patient whose initial cystoscopy was negative (diagnosis made of benign prostatic hypertrophy) and who had a repeat cystoscopy 4 months later which found a high-grade tumor (stage not reported).

DISCUSSION

This is the first randomized trial comparing a marker-based approach to evaluating hematuria with SOC. We found that in LR patients (by our definition pre-AUA 2020 guidelines) the CxbT result reduced the rate of cystoscopy from 67% to 27%. Indeed, those patients with a CxbT negative result had a cystoscopy rate of only 20%. Furthermore, the performance characteristics of CxbT was confirmed in the 270 patients having both CxbT and cystoscopy, showing a sensitivity of 90% and NPV of 99%. Finally, for those CxbT-negative patients who avoided cystoscopy only 1 bladder tumor was subsequently found over 1 year later, and this was presaged by a conversion of CxbT from negative to positive.

The approach to microhematuria is important due to the high prevalence of this finding in adults, as well as the significant but rare risk of potentially lethal malignancy. The current paradigm is problematic because the vast majority of adults with microhematuria fail to undergo any evaluation even if they have risk factors for bladder cancer including

Table 2. *Incidence of Cystoscopy in the Study Groups*

Groups	No. cystoscopies/No. subjects	Cystoscopy incidence		Change in cystoscopy incidence (%-points) Estimate (95% CI)
		First group	Second group	
LR test vs LR control	22/81 vs 36/54	0.27	0.67	−0.4 (−0.57:−0.22)
LR vs NLR	58/135 vs 209/255	0.43	0.82	−0.39 (−0.49:−0.29)
LR test Cxb− vs Cxb+	14/71 vs 8/10	0.20	0.80	−0.6 (−0.92:−0.28)

Abbreviations: CI, confidence interval; Cxb, Cxbladder; LR, lower risk; NLR, not lower risk.

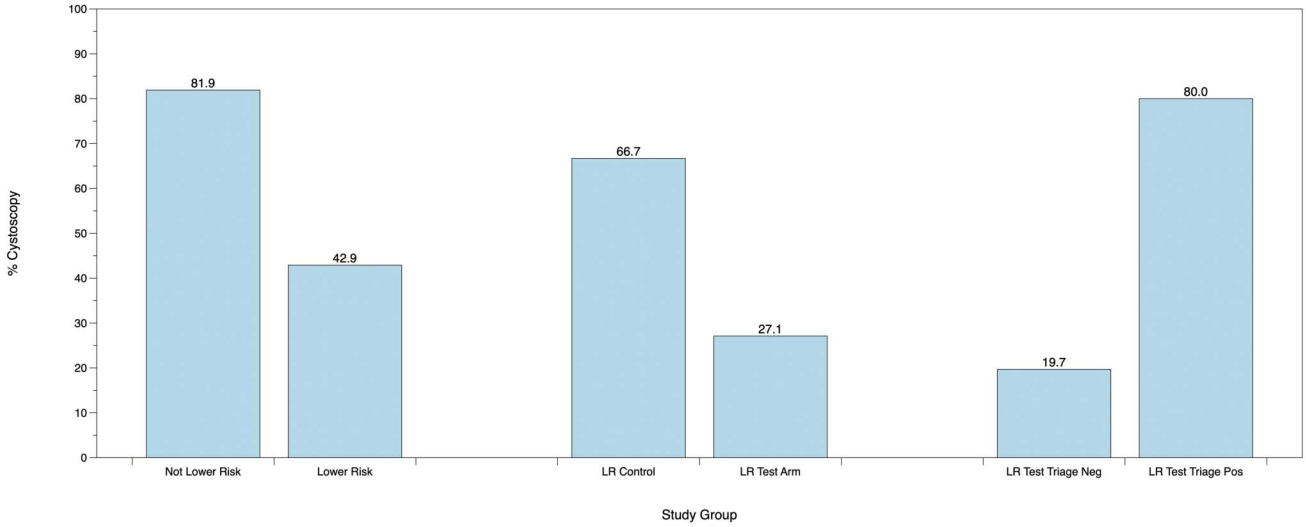

Figure 3. Comparison of cystoscopy rates between study groups. LR indicates lower risk.

age, sex, smoking, and occupational exposures. The AUA microhematuria guideline, which recommends cystoscopy for the majority of patients, is not followed consistently by primary care or other nonurologic physicians. The impact of the missed opportunity to detect bladder cancer is unknown but there has been no significant change in stage of diagnosis of bladder cancer in the last 30 years, suggesting that timing of detection has not improved. This is compounded by the lack of screening for the disease in high-risk patients. As such, the current paradigm for detecting bladder cancer in a timely fashion depends on timely referral for cystoscopy by referring physicians. An accurate urine-based tumor marker may offer a noninvasive method to detect bladder cancer, reduce unnecessary evaluations, and enrich evaluation with a population of patients at higher risk for having disease.

The historical and current paradigms for evaluating microhematuria are driven by concern for missing significant and potentially life-threatening UC, but result in a large proportion of unnecessary negative cystoscopies. Although it's a relatively benign and quick procedure, there is still a small but persistent incidence of iatrogenic urinary tract infection, trauma, false passage, and subsequent urethral stricture disease. In addition, patients report significant pain and anxiety.[11,12] There are also unmeasured costs of time off work, transportation, child care, and other burdens. There is finite access to clinic and procedure space, resulting in delays for patients with more serious pathology. Finally, there is the cost of all these negative cystoscopies, with significant medical waste and environmental footprint.[13] While UC is expected in no more than 5% of these patients, we have made little progress in reducing the burden for the 95% who could be managed noninvasively. The 2020 AUA guidelines first introduced the concept of offering low-risk patients the choice between cystoscopy and urinalysis surveillance, but in practice only 5% of patients referred to urologists actually fulfill the criteria for low risk.[5]

Table 3.

	Lower risk		Not lower risk		All		
CxbT result	Negative	Positive	Negative	Positive	Negative	Positive	Total
No UC, No.	57	17	82	93	139	110	249
UC, No.	0	1	2	18	2	19	21
Total, No.	57	18	84	111	141	129	270

Abbreviations: CxbT, Cxbladder Triage; UC, urothelial cancer.

One of the challenges with designing a randomized trial to evaluate a marker-based approach to hematuria is how to prove a negative. In prior clinical validation studies, all patients underwent cystoscopy and one could state that patients with a negative marker were "true" negatives and could have avoided cystoscopy. There are multiple such trials that all demonstrate a very high NPV for Cxbladder (>95%).[6-8] These trials are not prospective randomized controlled trials, and thus don't offer level 1 evidence. However, designing a pragmatic trial comparing a marker to cystoscopy requires the marker arm to either follow patients longitudinally to try to demonstrate that they don't develop bladder cancer over time or require every patient to undergo cystoscopy at some interval. It is impractical to convince patients to proceed with cystoscopy if they are at low risk of disease. Indeed, the cystoscopy rate in our NLR group was only 80% despite the recommendation by guidelines that all have the procedure done. There is an inherent limitation that a small number of cancers could be

unrecognized in a marker study. Prior data support the fact that if a cancer is missed then it most likely would be low grade.[7] In this study, there was 1 cancer discovered over a year later associated with the Cxbladder test becoming newly positive.

All of the tests in the Cxbladder suite are based on the mRNA expression of 5 genes, 4 related to growth and proliferation and 1 to inflammation.[8] Cxbladder Monitor is designed for nonmuscle-invasive surveillance,[14] Cxbladder Detect is designed for higher-risk hematuria patients seeing a urologist,[8] and CxbT is designed for low-risk hematuria patients, specifically calibrated to maximize NPV at the expense of specificity and positive predictive value to make it a useful rule-out test.[6] In the most recent study of 804 hematuria patients, CxbT had a sensitivity of 89%, an NPV of 99%, and a test negative rate of 59% for UC.[7] Indeed, incorporation of CxbT in a clinical pathway in New Zealand (which included gross hematuria) estimated a reduction of cystoscopy in about one-third of patients.[15] The tests can be done at home prior to the office visit, and patient compliance and satisfaction with the process is very high.[16] Innovations improving care often come at a cost, but a recent decision tree analysis actually calculated that using the Cxbladder Detect test to guide investigation of microhematuria reduced costs to payers by $559 per patient, on average, with no impact on the number of cancers diagnosed.[17]

There are several limitations to the study. The willingness of patients who did not have cystoscopy to return for follow-up was lower than expected, so in this study many didn't have the requested repeat CxbT values or ultrasounds. As previously mentioned, our risk stratification did not align with the current 2020 AUA microhematuria guidelines, and indeed many of our LR patients would be intermediate or even high risk (based on age alone) in the current guidelines. We cannot, therefore, give risk-specific performance data, either for outcomes or cystoscopy reduction, under the current AUA risk stratification scheme. We are beginning a clinical utility study for the enhanced Detect+ assay, which combines the mRNA markers with single nucleotide polymorphisms for FGFR3 and TERT gene mutations,[7] that will offer omission of cystoscopy for all microhematuria AUA risk groups. There was an unusually high number of patients whose complete data could not be source verified and was therefore lost to analysis. Finally, the 10 LR patients in the test arm who had a positive CxbT also were provided with their Cxbladder Detect result, a test that has a higher positive predictive value.[7] It is possible that without that additional information, some of the 8 patients who chose cystoscopy might not have.

In conclusion, in this prospective multicenter randomized controlled trial, use of CxbT to inform the decision for cystoscopy in patients with LR hematuria resulted in a 59% reduction in cystoscopy. This demonstrated clinical utility of CxbT to safely reduce the burden of unnecessary cystoscopies in this population, theoretically resulting in less patient morbidity and discomfort, improved access to care, and reduced environmental impact.

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EDITORIAL COMMENTS

I do approximately 500 office cystoscopies per year. Recently after performing a negative office cystoscopy for bladder cancer surveillance, I sent my patient out to the front desk to schedule their next one and they were told my "next available" cystoscopy slot was not for 6 months! (I overbooked him for 3 months). But this really got me thinking: how did we get to this place where clinic space and access have become such scarce resources? I doubt that my clinic is an outlier, having discussed similar issues with colleagues around the country.

Lotan and colleagues are doing important work to try and move the needle so we can spend our precious time and resources doing invasive procedures on patients where we are more likely to find something.[1] If I did 20 cystoscopies in clinic next week on index patients with microscopic hematuria, I would likely only discover something actionable in 1 patient. If one peruses Centers for Medicare & Medicaid Services claims data, there are roughly 800 to 900,000 cystoscopies (Current Procedural Terminology code 52000) done every year in the US, 20% of which are done for hematuria (based on diagnosis codes). Is there a way that we can identify which of those 180,000 patients benefit the most from office cystoscopy and which could avoid it?

The Cxbladder Triage test appears to be a step in the right direction. Its value is primarily its high negative predictive value (99%). None of the patients in the low-risk group had cancer if their Cxbladder Triage test was negative. It was also good to see that patients were open to omitting cystoscopy if their test was negative, suggesting that the real-world potential exists to roll this out. Given ongoing issues with access, space, and workforce, the time is right for strategies to eliminate waste in medicine and rethink our paradigms.

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When working up microscopic hematuria (MH), "it costs a lot to win, but even more to lose." Since the vast majority of patients who are evaluated for MH do not have any significant pathology found, the number needed to cystoscope/image (and the cost) to find a single cancer remains unacceptably high.[1] Conversely, patients diagnosed with bladder cancer during asymptomatic MH evaluations have traditionally been

lower stage than those with symptoms or found as part of gross hematuria workups. As a field, I think we can safely agree that there is a benefit to remaining proactive about finding bladder cancers. However, due to an absence of high-level data to help guide our diagnostic efforts toward those at highest risk, we remain in the unenviable situation we're currently in.

Lotan and colleagues report the results of a recent multicenter randomized study that aims to at least partially address this problem.[2] Using Cxbladder Triage, a commercially available urinary assay that helps predict the likelihood of discovering a urothelial carcinoma with cystoscopy for patients with MH, they demonstrate that providing the results of this assay to patients and urologists reduced the number of cystoscopies performed by 59% without any significant "missed" cancers. Secondarily, they also further validate the strong negative predictive value of the assay in this setting as another step toward wider use.

The authors should be commended for these efforts and for the important contribution to the literature. However, any potential biomarker that may be used in the MH setting will have an exceedingly high bar to cross before truly effecting a change in practice. We already know that only a small but select subset of patients with MH are ever referred for evaluation—these tend to be older, male patients, who have risk factors for bladder cancer, such as a significant smoking history. Even among this enriched cohort of referred patients, bladder cancer is found in ~1% of all comers. So, if in the future no patients with MH ever receive an evaluation, we could similarly and correctly avoid cystoscopies without any missed cancer in 99% of them—this is what we're up against.

While this extreme example simply reflects the basics of diagnostic testing and disease prevalence, it suggests that our efforts may be best spent working toward developing a population-level screening strategy, which may include helpful urinary biomarkers like Cxbladder, as a means of identifying patients at highest risk of having early-stage occult bladder cancer. Beyond being a far more systematic approach to diagnosing bladder cancer than the current "Swiss cheese" model of evaluating whoever ends up on your clinic schedule, this strategy would have the additional benefit of promoting a more equitable and optimal use of resources given all that we know about disparities in our current approach to the evaluation of MH.[3]

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REPLY BY AUTHORS

Among patients with microhematuria referred to urologists, the rate of cancer ranges between 0.4% and 2.6% depending on risk factors (age, smoking intensity, sex).[1] Unfortunately, there are significant inconsistencies with referrals to urologists and many patients at risk of harboring disease are not adequately evaluated. This represents a missed opportunity for early detection of bladder cancer. While the low prevalence of disease means that any test including no testing would have a high negative predictive value, it misses the potential benefits of a high-performing test. In this study, the Cxbladder Triage test had a 99% negative predictive value and reduced cystoscopies by 59%.[2] However, equally importantly, the test found the only cancer in the lower-risk group and all the high-grade cancers in the entire cohort, missing only 2 low-grade cancers.

The current status quo for bladder cancer detection has resulted in 25% of patients presenting with muscle-invasive bladder cancer or metastatic disease with approximately 50% survival at 5 years. Unless we improve detection either by screening or changing the paradigm around hematuria evaluation, this is unlikely to change. Incorporating a urine marker to enrich referral of higher-risk patients (either based on clinical or biologic factors) could benefit many patients who would otherwise not be referred and avoid cystoscopy in many who are getting unnecessary testing.

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