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AUA Guideline Articles

Updates to Microhematuria: AUA/SUFU Guideline (2025)

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Purpose: In 2023 the AUA in collaboration with the Society for Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU) requested an Update Literature Review to incorporate new evidence generated since the 2020 publication of this Guideline. The resulting 2025 Microhematuria Guideline Amendment addresses updated recommendations to provide a clinical framework for the diagnosis, evaluation, and follow-up of microhematuria.

Materials and Methods: In 2024, this Guideline was reviewed via the AUA Update Literature Review process, which identified 82 studies for full-text review that were published between December 2019 and June 7, 2024. Of those 82 studies, 23 met inclusion criteria for qualitative synthesis. The subsequent amendment is based on data released since the initial 2020 publication of this Guideline.

Results: The Panel developed evidence- and consensus-based statements based on an updated review to provide guidance on evaluation and management of microhematuria. These updates are detailed herein.

Conclusions: This update provides several new insights, including a revised risk stratification system, updated information regarding use of urine-based tumor

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markers and cytology, and new guidance on diagnosis and surveillance. This Guideline will require further review as the diagnostic and treatment options in this space continue to evolve.

Key Words: hematuria, cystoscopy, CT urogram, bladder cancer, urothelial carcinoma, urine markers

BACKGROUND

Hematuria remains one of the most common urologic diagnoses, estimated to account for over 20% of urology evaluations.[1] Indeed, screening studies have noted a prevalence range of microhematuria (MH) among healthy volunteers of 2.4% to 31.1% depending on the specific population evaluated.[2] Urologic etiologies for hematuria include malignancy, infection, inflammation, calculus disease, benign prostatic hyperplasia, and congenital or acquired anatomic abnormalities.[3] While most experts agree that patients with gross hematuria (GH) should be evaluated with cystoscopy, upper tract imaging, and urinary cytology, significant variability exists across current guidelines and consensus statements regarding MH, particularly the definition of MH, criteria for evaluation, as well as the appropriate components of the evaluation, including the optimal imaging modality.[4,5]

The underuse of cystoscopy, and the tendency to solely use imaging for evaluation, is particularly concerning when one considers that most cancers diagnosed among persons with hematuria are bladder cancers, optimally detected with cystoscopy.[6] Delays in diagnosis of bladder cancer have been suggested to contribute to a 34% increased risk of cancer-specific mortality and a 15% increased risk of all-cause mortality.[7] As such, the need exists to develop and disseminate clear guideline recommendations for evaluation of hematuria that limit the unnecessary risks and costs associated with the over-evaluation of patients who are at low risk for malignancy, while at the same time addressing the delays in diagnosis of important urologic conditions caused by widespread under-evaluation and variations in care.

An updated risk stratification system has been detailed in Table 1. A summary of diagnostic and treatment recommendations may be found in the Algorithm (Figure).

GUIDELINE STATEMENTS

Initial Evaluation

In patients with MH, clinicians should perform a history, physical examination including blood pressure measurement, and serum creatinine to assess risk factors for genitourinary malignancy (e.g., detailed smoking history), medical renal disease, gynecologic, and non-malignant genitourinary causes of MH. (Clinical Principle)

A detailed history and physical examination should be performed in patients who are confirmed to have MH. Important aspects of the history should include age, sex, history of GH, irritative urinary symptoms, and overall health status. Careful consideration should be given to risk factors for malignancy, with specific emphasis on assessing for family history of urologic malignancies, and genetic or other risk factors for bladder or urothelial cancer, such as environmental/occupational exposures. Due to the causal association between tobacco use and both bladder and kidney cancer, a detailed tobacco exposure history should be performed at the initial

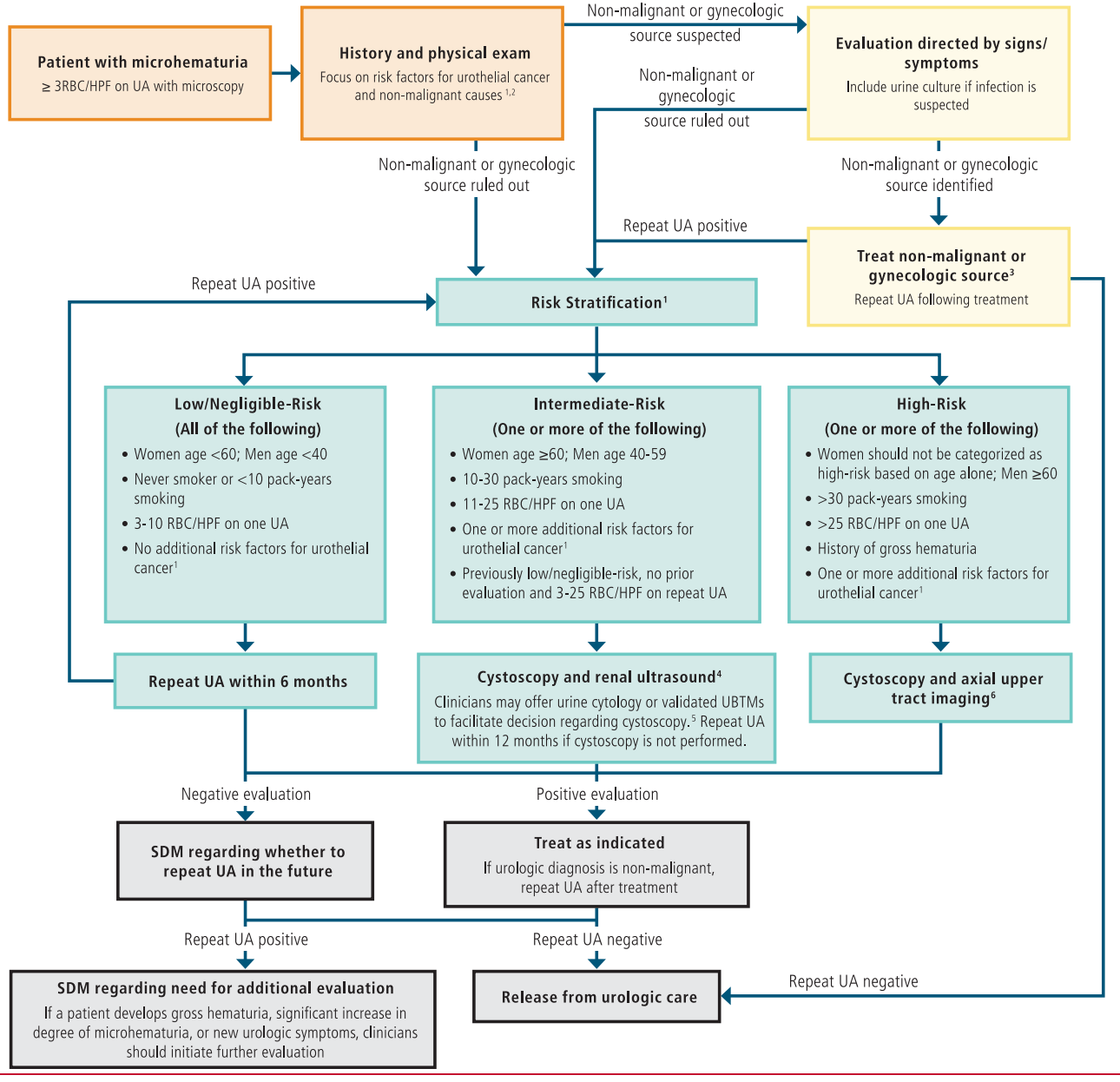
Table 1. *AUA/SUFU Microhematuria Risk Stratification System 2025*

Risk of malignancy[a]	Low/negligible 0%-0.4%[8-10]	Intermediate 0.2%-3.1%[8-10]	High 1.3%-6.3%[8-10]
Number of criteria patient must meet	All	One or more	One or more
Degree of hematuria on a single urinalysis	3-10 RBC/HPF$^+$	11-25 RBC/HPF$^+$	>25 RBC/HPF$^+$
Alternative criteria for degree of hematuria		Previously low/negligible-risk patient with no prior evaluation and 3 to 25 RBC/HPF[a] on repeat urinalysis	History of gross hematuria
Age for women	<60 y	≥60 y	*Women should not be categorized as high-risk solely based on age*
Age for men	<40 y	40-59 y	≥60 y
Smoking history	Never smoker or <10 pack years	10-30 pack years	>30 pack years
Presence of additional risk factors for urothelial cancer (see Figure, Footnote 1)	None	Any	One or more plus any high-risk feature

Abbreviations: HPF, high-power field; RBC, red blood cells.

[a] Risk of malignancy is based on the definition from the 2020 AUA/Society for Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction Guideline in which women being age < 50 y was a criterion for low-risk, women being age 50 to 59 y was a criterion for intermediate-risk, and women being age > 60 was a criterion for high-risk. Based on interval studies showing significantly lower risk of urothelial malignancy in women, women being age < 60 is a criterion for low-risk, women being age > 60 y is a criterion for intermediate-risk, and women cannot be categorized as high-risk based on age alone in the 2025 guideline iteration.

AUA/SUFU Microhematuria Diagnostic Algorithm



1. Additional risk factors include but are not limited to the following:
   - irritative lower urinary tract symptoms
   - prior pelvic radiation therapy
   - history of cyclophosphamide/ifosfamide chemotherapy
   - family history of urothelial carcinoma or Lynch syndrome
   - occupational exposure to benzene chemicals or aromatic amines
   - chronic indwelling foreign body in the urinary tract.

   Note, risk stratification and risk-based evaluation are the same for those on anti-platelet and anti-coagulation therapy as for those who are not.
2. If medical renal disease is suspected, consider nephrological evaluation, but pursue concurrent risk-based urologic evaluation.
3. There are non-malignant and gynecologic sources of hematuria that do not require treatment and/or may confound the diagnosis of microhematuria. Use careful judgment and patient engagement to decide whether to pursue microhematuria evaluation in the setting of such conditions.
4. Clinicians may perform cross-sectional imaging with urography or retrograde pyelograms if hematuria persists after negative renal ultrasound.
5. Intermediate-risk patients who decline cystoscopy following UBTMs should still undergo renal and bladder ultrasound.
6. MR urogram or non-contrast imaging plus retrograde pyelograms if contraindications to CT urogram.

HPF: high-power field
RBC: red blood cell
SDM: shared decision-making
UA: urinalysis
UBTM: urine-based tumor marker

Figure. AUA/SUFU microhematuria diagnostic algorithm.

consultation and should include smoking intensity (pack-year quantification) and other tobacco product usage to aid with risk stratification. For patients who currently smoke or use other tobacco products, clinicians should assist with cessation by providing a recommendation to quit and facilitating evidence-based smoking cessation treatment through institutional or other publicly available resources.[11] Of note, the association between bladder cancer and non-combustible tobacco products such as heat-not-burn devices or electronic cigarettes is not well established at this time. However, patients who use non-combustible tobacco products have significant levels of urinary carcinogens and metabolites of exposure that are associated with bladder cancer development.[12] Physical examination should include measurement of blood pressure and a genitourinary examination as dictated by clinical history.

Risk Assessment

Following initial management, clinicians should categorize patients presenting with MH as low/negligible-, intermediate-, or high-risk for genitourinary malignancy (Table 1). (Strong Recommendation; Evidence Level: Grade C)

The risk stratification system in the 2020 AUA/SUFU Guideline was based on a systematic review of the literature on risk factors for urothelial cancer and several publications on risk stratification systems. Since 2020, several groups have sought to validate the AUA/SUFU risk stratification system, determine the actual risk of malignancy in each risk stratum, and assess if the risk stratification approach reliably discerns unique risk to patients. This Guideline revision aims to refine the risk stratification system and risk-based evaluation recommendations to align with the findings of these validation studies.

Sanci et al conducted a retrospective study of 1018 men and women who presented with MH, defined as 3 or more red blood cells (RBC)/high-power field (HPF) on urinalysis (UA) with microscopy in the absence of an obvious benign cause.[13] All patients were evaluated according to the older 2012 AUA Guideline and underwent cystoscopy and urinary tract imaging (96.2% had CT urography). Overall, urinary tract malignancy was detected in 34 patients (3.3%), of which 32 (94%) had low-grade Ta and 2 (6%) had high-grade T1 urothelial carcinoma. Retrospectively, patients were risk-stratified according to the 2020 AUA/SUFU system, and 21.4% were low-risk, 43.9% were intermediate-risk and 34.6% were high-risk. No cancers (0%) were detected in the low-risk group (n = 218). Among 447 intermediate-risk patients, 14 (3.1%) were diagnosed with urothelial cancer, and among 353 high-risk patients, 20 (5.7%) were diagnosed with urothelial cancer. Thus, the risk of malignancy in this cohort did vary according to AUA/SUFU risk-stratum. Notably, however, no malignancies were identified in the low-risk group, suggesting that their risk is negligible.

Woldu et al compiled a dataset of 15,779 patients with MH from 5 clinical trials of urinary biomarkers and 2 prospective registries and compared bladder cancer detection across 2020 AUA/SUFU risk categories.[14] Of note, all the included studies contained a subset of patients presenting with GH who were included in the high-risk group, which may have inflated the cancer detection rate in that risk stratum. Furthermore, there was a lack of granularity regarding degree of MH, number of pack-years of smoking, and use of imaging. Among the 15,779 patients, all of whom underwent cystoscopy, there were 857 bladder cancers diagnosed (5.4%, ranging among source cohorts from 2.3% to 11.5%). Of the 727 (4.6%) patients categorized as low-risk, 3 patients (0.4%) were diagnosed with bladder cancer. In the 1863 (11.8%) intermediate-risk patients, 18 cancers (1.0%) were detected. Finally, of the 13,189 (83.6%) high-risk patients, 836 (6.3%) were diagnosed with bladder cancer. Among the high-risk group, 2.6% of those with solely MH (ie, without GH) had bladder cancer, while 10.9% of those with GH had bladder cancer. Although the percentage of patients with cancer in the intermediate- and high-risk strata was lower than in the Sanci study, the risk of malignancy varied by risk stratum and, similar to the Sanci study, cancer incidence among patients in the low-risk category was extremely low.

Lastly, Saxon et al conducted a retrospective study of 1730 women evaluated in a university-based urology practice for MH.[15] Of note, 431 or 31.3% of women included in the study were considered inappropriate referrals because they were diagnosed on dipstick alone or had < 3 RBC/HPF on UA with microscopy. Of the 1730 patients, 864 "appropriate" evaluations were performed. A total of 13 genitourinary malignancies were identified, 9 renal cell carcinomas (RCC), and 4 bladder cancers. Assuming that these were all among the patients who were considered appropriate for evaluation, this is a detection rate of 1.5%. Malignancy detection rate was 0% among 322 (18.6%) low-risk patients; 0.2% (n = 1) among 463 (26.8%) intermediate-risk patients; and 1.3% (n = 12) among 945 (54.6%) high-risk patients. While the detection rate may be somewhat diluted by the high proportion of patients who were referred and/or evaluated inappropriately, this study also shows variation in cancer detection rate by risk stratum, with risk being extremely low in the low-risk category. Furthermore, the investigators found that 11 of the 13 malignancies were diagnosed in women over the age of 60, indicating

that the risk of malignancy in younger women is quite low. Interestingly, 12 of the 13 malignancies were identified in women with 3 to 10 RBC/HPF on UA, while 1 was found in a woman with 11 to 25 RBC/HPF and none in women with > 25 RBC/HPF. This indicates that evaluation is justified in women with lower degrees of MH, provided that other risk factors, particularly age, are present. Additionally, almost 70% of malignancies were observed in the kidney, underscoring the importance of imaging the upper tract.

Collectively, these studies validate the 2020 AUA/SUFU risk stratification system to define distinct groups that have varying degrees of risk of genitourinary malignancy. However, they also justify several important changes to the risk stratification system. First, women under the age of 60 have a very low risk of malignancy in the absence of other risk factors. Thus, the Panel changed the age range for women in the low-risk group from < 50 years to < 60 years and similarly changed the age range for women in the intermediate-risk group from 50 to 59 years to ≥ 60 years. Second, to account for the lower risk of malignancy in women, the risk groups have been updated such that women should not be characterized as high-risk based on age alone. As such, they should be categorized as high-risk only if one or more of the other high-risk criteria are present.

The Panel notes that the proposed risk stratification system is imperfect. For example, it groups together the risk of urothelial malignancy with other urologic cancers while the risk factors are primarily those for bladder cancer. A risk categorization system for renal cortical neoplasms among people with MH may look quite different. Furthermore, the risk stratification system weighs different risk factors such as smoking and degree of hematuria equally, though they may contribute differently to risk of malignancy. To account for the differential weighting of various risk factors, some have proposed and developed nomograms or calculators to estimate an individual's risk for malignancy.[16,17] Each of these has its strengths and limitations; while none of these has been sufficiently validated to recommend for regular use, there may be instances in which such estimates could influence decision-making.

Risk-Based Evaluation

Low/Negligible-Risk.

In low/negligible-risk patients with MH, clinicians should obtain repeat UA within six months rather than perform immediate cystoscopy or imaging. (Moderate Recommendation; Evidence Level: Grade C)

The Sanci, Woldu, and Saxon studies, intending to validate the 2020 AUA/SUFU risk stratification system, found extremely low rates of malignancy among patients in the low-risk category (0%, 0.4%, and 0%, respectively).[13-15,18] Additionally, the Sanci study followed low-risk patients for a median of 26 months, and no additional cancers were identified. Thus, given the low risk of malignancy and the potential harms of over-evaluation, the Panel recommends against routine cystoscopy and imaging for the initial evaluation of patients in the low-risk category and has renamed the category as low/negligible-risk to emphasize this point. The Panel acknowledges, however, that there may be scenarios in which cystoscopy in low/negligible-risk patients may be warranted based on symptoms, clinical suspicion, or patient preference. Notably, given the intermittent nature of hematuria (both with regards to presence and degree), the Panel does recommend a repeat UA with subsequent risk-based evaluation predicated on those results.

Initially Low/Negligible-Risk With Hematuria on Repeat UA.

Low/negligible-risk patients with MH on repeat UA should be reclassified as intermediate- or high-risk based on repeat UA. In such patients, clinicians should perform risk-based evaluation in accordance with recommendations for these respective risk strata. (Strong Recommendation; Evidence Level: Grade C)

Low/negligible-risk patients should undergo a repeat UA to evaluate for the resolution vs persistence of MH. A study of over 11,000 patients from a large public health system determined that patients with persistent MH on repeat urine testing had a significantly higher rate of malignancy on subsequent evaluation as compared with those who had negative repeat urine testing (0.35% vs 0.07%).[19] If the repeat UA shows no evidence of MH, then no further evaluation of the bladder or upper tract is needed at this time. In that case, further evaluation is only merited if new symptoms, more severe MH on subsequent opportunistic testing, or GH develop. If the patient experiences recurrence of a similar level of MH (3-10 RBCs/HPF) on subsequent opportunistic testing, further evaluation may be considered in a shared decision-making (SDM) process.

Intermediate-Risk.

Clinicians should recommend cystoscopy and renal ultrasound in patients with MH categorized as intermediate risk for malignancy. (Strong Recommendation; Evidence Level: Grade C)

Studies of MH patients have consistently demonstrated that bladder cancer is the most frequently detected urologic malignancy during evaluation.[6] As such, cystoscopy should be recommended for bladder evaluation in intermediate-risk MH patients. Notably, Tan et al explored the ability of renal-

bladder ultrasound in conjunction with a risk index (Hematuria Cancer Risk Score) to inform use of cystoscopy in hematuria patients.[20-22] In their validation cohort (27% with MH), the sensitivity for identification of bladder cancer was 97% with 117 patients (25%) theoretically avoiding cystoscopy at the cost of missing a single patient of G1 Ta bladder cancer. While these observations are compelling, the cohort included a relative minority of patients with MH. As such, cystoscopy is still currently the preferred recommendation for MH evaluation in intermediate- and high-risk patients.[8,22,23]

The goal of upper tract imaging in MH patients is to identify malignancies of the renal parenchyma and upper tract urothelium as well as to identify actionable non-malignant diagnoses of the kidney, collecting system, and ureters. Admittedly, the overall risk of renal parenchymal cancer and upper tract urothelial carcinoma (UTUC) is low. Kang et al[9] determined that among 911 patients with MH, only 3 (0.3%) had upper tract malignancy—all RCC. Meanwhile, a Samson et al[24] study of 1049 patients with MH found 1 patient (0.1%) with UTUC and 2 patients (0.2%) with RCC, while the Matulewicz et al[6] series of 15,161 patients with MH noted only 96 patients (0.6%) with an upper tract malignancy. Additionally, the DETECT I study reported only a 1.7% incidence in a mixed cohort of MH and GH, and Fankhauser et al noted an even lower 0.7% incidence in a pure MH cohort (n = 432).[10,20] Thus, the choice of imaging is guided by the patient's risk category, which seeks to balance diagnostic accuracy vs risk.

CT urography provides excellent delineation of the excretory urinary tract, is very sensitive for urinary stones, readily identifies renal cortical lesions, and provides extra-urinary information.[25] However, CT urography is generally more expensive than renal ultrasound and involves ionizing radiation and iodine-based IV contrast. Renal ultrasonography is relatively less expensive, does not involve ionizing radiation, and has reasonable discrimination for cortical lesions, although image quality is dependent on operator experience and the patient's body habitus. Importantly, optimal bladder distension is necessary for radiographic bladder cancer assessment. With a lack of bladder distention, smaller tumors may not be visible secondary to detrusor folds or detrusor muscle thickening.[26]

In the study by Fankhauser et al, performance characteristics for ultrasonography for detection of UTUC and renal cortical tumors included sensitivity of 33%, specificity of 96%, positive predictive value of 6%, and negative predictive value (NPV) of 100%.[10] Prior studies note that for UTUC, the sensitivity of CT urography has been reported to be 94%, compared with 14% for renal ultrasound.[22] Additional studies evaluating CT urography reported adequate sensitivity for detection of both cortical tumors (100% sensitivity) and UTUC (80%-99% sensitivity).[27-29] While CT urography offers the most sensitive detection of upper tract malignancy,[4] use of this modality must be balanced with the overall low rate of upper tract malignancy in MH patients[30] as well as the potential harms associated with CT, including ionizing radiation, IV contrast reactions, and false-positive results.[20,31-33]

Collectively, the Panel believes the risk of RCC and UTUC is low enough in the intermediate-risk group that the balance of benefits and harms of imaging favors renal ultrasound over cross-sectional imaging. While less intense evaluation (eg, renal ultrasound) risks missing a very small number of upper tract malignancies compared to a more intense evaluation (eg, CT), routine use of renal ultrasound instead of CT urography for intermediate-risk patients would decrease costs, complications of iodinated contrast, and patient radiation exposure.[20]

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 (Table 2) to facilitate the decision regarding utility of cystoscopy. Renal and bladder ultrasound should still be performed in these cases. (Conditional Recommendation; Evidence Level: Grade C)

The gold standard to evaluate for bladder cancer is cystoscopy, but urine-based tumor markers (UBTMs) and urine cytology were developed to provide a non-invasive method to detect urothelial carcinoma. A systematic review of the literature evaluated the performance of cytology and commercially available UBTMs and included 11 studies with study populations of 8302 patients for cytology evaluation and a range of 354 to 6474 patients for the commercially available UBTMs.[18] Likelihood ratios (LR), which represent the relative likelihood of cancer presence, were calculated. A LR of ~1 indicates a test is not capable of changing the post-test probability of disease. A positive LR > 1 increases probability of disease in the presence of a positive test, while a negative LR < 1 decreases the probability of disease in the presence of a negative test. In this analysis, the positive LR for cytology was 7.67 while the negative LR was 0.35. For other UBTMs, positive LR ranged from 2.14 to 6.6, while the negative LR ranged from 0.07 to 0.48.

The role of urine cytology or UBTMs is to assist in cases where the test results may inform the added

value of performing cystoscopy. For low/negligible-risk cases where the risk of bladder cancer is approximately 0.4%,[14] the use of cytology and UBTMs would be exceptionally unlikely to identify any cancers and would be more likely to increase the risk of unnecessary evaluations attributable to false-positive results. Conversely, in high-risk patients, the incidence of cancer exceeds 2.5%,[13-15] and there is insufficient evidence that use of cytology or UBTM would safely obviate the need for cystoscopic evaluation of the bladder.

In patients with intermediate-risk disease, where the baseline prevalence of malignancy is approximately 1% (0.2%-3.1%), the high NPV of most markers would result in a low likelihood of cancer in patients with negative marker evaluations.[13-15,18] For example, based on the above-mentioned LR of cytology, a patient with a 1% pre-test probability of bladder cancer would have a post-test probability of 0.4% in the setting of a negative cytology. Similarly, a negative test on other UBTMs can reliably re-stratify a patient who might be otherwise classified as intermediate-risk into a low/negligible-risk category, with the (post-test) probability of cancer detection decreasing to 0.1%-0.4%.

Currently, the strength of evidence regarding different urine markers and cytology is highly variable. Most of the studies evaluating urine markers were performed in mixed populations (MH and GH). Since patients with a history of GH are classified as high-risk, the Panel focused on studies comprised of a hematuria population whereby at least 25% were MH with at least 100 MH patients. The principal outcome of interest was NPV given the theoretical intent of identifying patients who can safely avoid cystoscopy with a lower risk of missing cancer.[34] The highest level of evidence was a randomized controlled trial comparing a marker-based approach with CxBladder Triage vs standard of care, that is, routine cystoscopy, to evaluate MH. In this study, the marker had a NPV of 99%. Several other UBTMs and urine cytology also had reported NPV of 95% to 100% in the target population (Table 2).

Patients with intermediate-risk MH who choose to forego cystoscopy based on the results of UBTM or cytology should still be evaluated with a renal and bladder ultrasound to evaluate the upper tract and renal parenchyma. While UBTM and cytology have a role in determining which patients can safely avoid cystoscopy, the potential upper-tract pathologies including (but not limited to) larger or obstructing UTUC, renal cortical tumors, hydronephrosis, and nephrolithiasis merits investigation with imaging.

For patients with intermediate-risk MH who do not undergo cystoscopy based on urinary marker results, clinicians should obtain a repeat UA within 12 months. Such patients with persistent MH should then undergo cystoscopy. (Strong Recommendation; Evidence Level: Grade C)

The STRATA study aimed to evaluate whether a UBTM (CxBladder Triage) could help identify patients with MH at high risk of having bladder cancer while also safely avoiding evaluation in those with a negative marker result. Specific to this statement, for those deemed "lower-risk" (defined as a 3-29 RBC/HPF and up to a 10 pack-year smoking history) who had a negative marker and did not undergo cystoscopy (n = 57), follow-up renal/bladder ultrasound, urine cytology, and repeat UBTM were offered. This resulted in the detection of 1 subsequent pTa high-grade bladder cancer diagnosis 13 months after initial presentation,[34] though subsequent follow up evaluation and data availability among all patients was not uniform. Given that the data supporting the use of UBTM remains nascent, the Panel believes that a repeat UA within 12 months should be considered, primarily for safety, with persistent MH on subsequent UAs prompting a recommendation for cystoscopy.

Table 2. *Reported Negative Predictive Values for the Detection of Bladder Cancer Using the Available Urine Cytology and Urine-Based Biomarkers*[a]

Assay[A]	Hematuria population	Total patients (n)	Reported negative predictive value	AUA strength of evidence[B]
CxBladder Resolve	MH and GH	Total n = 548; MH n = 289	99.8%[98]	B
CxBladder Triage	MH[C]	n = 390	99%;[97] 95% CI: 95%-100%[D]	A
	MH and GH	Total n = 571; MH n = 185	100%;[99] 95% CI: 94%-100%[E]	C
NMP22 BladderChek (qualitative)	MH	n = 876	95%-100%[100-102]	C
Urine cytology	MH	n = 513	95.0%-98.7%[100,103,104]	C
	MH and GH	Total n = 4497; MH n = 1743	89.5%[F]-96.0%[77,105-107]	C
UroVysion	MH and GH	Total n = 828; MH n = 384	97%[105]	C
Xpert	MH and GH	Total n = 1152; MH n = 597	98.0%-99.6%[105,106]	C

Abbreviations: GH, gross hematuria; MH, microhematuria.

[a] (A)To be included in the table, NPV for the assay was reported in a purely MH population or MH patients comprised ≥ 25% of total hematuria population. All studies included ≥ 100 microhematuria patients. (B) Strength of evidence in relation to reported NPV. Refer to full AUA MH Guideline for strength of evidence definition and methodology. (C) The RCT[97] is the only identified study designed to evaluate use of a urine-based biomarker to guide evaluation. (D) NPV for detection of high-grade disease[97], 100%; 95% CI: 97%-100%. NPV for lower risk patients, 100%; 95% CI: 94%-100%. (E) NPV reported for MH subgroup.[99] (F) NPV of 89.5%[107] reported for detection of bladder cancer and UTUC.

The recommendation specifically for repeat UA among those who choose not to initially undergo a cystoscopy is based on a 2021 Pak et al[35] study in which 637 patients with initial negative evaluations underwent repeat evaluation due to persistent or recurrent MH. In this study, 1.2% of patients were found to have a bladder tumor.

These patients should already have been evaluated with renal and bladder ultrasound at initial presentation, and further evaluation of the upper tracts with cross-sectional imaging (eg, CT urography) could be considered. For patients with a negative follow-up UA, clinicians should engage in SDM regarding whether to repeat UA in the future.

High-Risk.

In patients with MH who have a family history of renal cell carcinoma, a known genetic renal tumor syndrome (Table 3), or a personal or family history of (or suspicious for) Lynch syndrome, clinicians should perform upper tract imaging regardless of risk category. (Expert Opinion)

RCC is associated with several genetic syndromes[36] and with a family history of RCC.[37] Furthermore, patients with a personal or family history of Lynch syndrome (also known as hereditary nonpolyposis colon cancer or HNPCC) are at increased risk for UTUC, among other malignancies. Thus, the Panel believes that patients with MH who have such a history warrant upper tract imaging regardless of risk classification. As insufficient evidence exists regarding the preferred modality in this scenario, the choice of imaging remains at provider discretion, although CT or MR urography or RPG would be preferred in Lynch syndrome[38] (Table 3).

Urinary Markers

Clinicians should not routinely use urine cytology or urine-based tumor markers to decide whether to perform cystoscopy in the initial evaluation of low/negligible- or high-risk patients with MH. (Strong Recommendation; Evidence Level: Grade C)

Clinicians should not routinely use cytology or urine-based tumor markers as adjunctive tests in the setting of a normal cystoscopy. (Strong Recommendation; Evidence Level: Grade C)

Table 3. *Inherited Risk Factors for Renal Cortical Tumors*

Known genetic renal tumor syndrome
1. von Hippel-Lindau
2. Birt-Hogg-Dube
3. Hereditary papillary RCC
4. Hereditary leiomyomatosis RCC
5. Tuberous sclerosis

Abbreviations: RCC, renal cell carcinoma.

Low/negligible-risk patients have a very low probability of harboring cancer; as such, the use of cytology or UBTMs in their initial evaluation would lead to identification of very few cancers with a large number of avoidable cystoscopy evaluations even if those tests had very high sensitivity and specificity. Conversely, for high-risk patients, the overall incidence of cancer is relatively high. At present, there is insufficient evidence to demonstrate the safety and efficacy of using cytology or UBTM results to exclude the need for cystoscopy in the initial evaluation of high-risk patients.

While the current Guideline finds potential value in using cytology and UBTMs in patients with intermediate-risk MH as part of SDM, this does not extend as an adjunctive diagnostic test in addition to cystoscopy for the evaluation of patients with MH. The additional value of these tests in the setting of a negative cystoscopy during an initial evaluation of MH is unsupported by the current literature since the NPV of cystoscopy alone is very high. For example, a prospective study of 2778 patients evaluated the added benefit of obtaining cytology during the initial evaluation of MH.[39] Of the 2778 patients, only 2 with a negative evaluation (cystoscopy, ultrasound and IV pyelogram) and a positive cytology were eventually diagnosed as having urothelial carcinoma. In addition, there are risks and financial toxicity associated with the 10.5% false-positive rate from cytology in this study, as these patients will often undergo additional evaluations.

Likewise, a study of urine cytology obtained from 660 patients noted that a positive cytology detected urothelial carcinoma in only 4 patients with normal cystoscopy, of whom 2 had carcinoma in situ (CIS) and 2 had upper tract disease. Meanwhile, the DETECT I study recruited 3556 patients presenting with hematuria (30.3% MH, 69.7% GH), of whom urine cytology was performed in 567 (15.9%).[20] A positive/atypical urinary cytology was reported to have a sensitivity of 57.7%, specificity 94.9%, positive predictive value 35.7%, and NPV 97.9%, with an ROC of 0.688. Moreover, no bladder cancer or UTUC was diagnosed based on a suspicious urinary cytology test alone. Twenty-two patients had a positive urinary cytology result despite a normal cystoscopy and upper tract imaging. Twelve patients (54.5%) had a further diagnostic procedure in the form of ureteroscopy with/without biopsy (n = 5) or interval cystoscopy (n = 7). No bladder cancer, ureteral, or renal pelvis UTUC was identified. Five patients (22.7%) underwent repeat urinary cytology, which was normal.

Similarly, while UBTMs have been evaluated in conjunction with cystoscopy in the hematuria setting, studies have not evaluated the likelihood of

cancer in the setting of a normal cystoscopy.[40] Collectively, therefore, data currently indicate that cytology rarely identifies cancer in the setting of normal cystoscopy and imaging and data are lacking for UBTMs in this space.

Clinicians may obtain urine cytology for high-risk patients with equivocal findings on cystoscopic evaluation or those with persistent MH and irritative voiding symptoms or risk factors for carcinoma in situ after a negative workup. (Expert Opinion)

One area for which cytology may have a role is in improving detection of CIS. CIS is often associated with irritative voiding symptoms, and it has been recognized that white light cystoscopy may fail to identify some bladder cancers, especially CIS.[41] In a prospective cohort study enrolling MH and GH patients, the diagnostic sensitivity of cytology was 57.7% (95% CI: 38.7-75.3) for high-risk bladder cancers.[20] As such, there may be a role for cytology in high-risk patients with persistent MH after negative evaluation or in other scenarios in which clinical suspicion for CIS is high due to risk factors such as irritative voiding symptoms. Additionally, there may be a role for cytology in adjudicating cases of high-risk patients with equivocal cystoscopic evaluation to decide whether to perform biopsy.[40]

Thus, while there is a lack of convincing evidence for its routine use, there are instances in which clinical suspicion for CIS is sufficiently high that urinary cytology may be warranted as an adjunctive test.

Follow Up

In patients with a negative risk-based hematuria evaluation, clinicians should engage in SDM regarding whether to repeat UA in the future. (Strong Recommendation; Evidence Level: Grade C)

Most patients who have an appropriate risk-stratified negative hematuria evaluation do not require ongoing urologic monitoring and may be safely discharged from the urology practice after SDM and discussion of the best available evidence. After a negative MH evaluation and in the absence of a change in clinical condition (eg, GH, new symptoms), repeated evaluation has minimal diagnostic yield. However, the Panel recognizes that select patients (eg, those with multiple risk factors or a heavy smoking history) may benefit from and/or request follow-up after a negative hematuria evaluation. For these patients, a future UA may be considered.

In situations where ongoing follow up after a negative hematuria evaluation is desired following SDM, the Panel recommends obtaining a repeat UA with microscopy. This simple, non-invasive test provides quantitative information about the degree of MH. Patients who have a negative repeat UA after a negative MH evaluation do not need further MH follow up. However, even among patients with persistent or recurrent MH, the incidence of malignancy is low, and these cancers are diagnosed years after the initial evaluation. In the aforementioned Pak et al study, repeat cystoscopy in 161 of the 637 patients with a negative evaluation and persistent or recurrent MH revealed 2 new bladder cancers (1.2%), while repeat imaging detected a new suspicious renal mass in 4 of 317 patients (1.3%). Notably, both the bladder and renal cancers were detected more than 36 months following the initial evaluation.[35]

If a complete MH evaluation reveals a benign etiology not requiring intervention (eg, enlarged prostate with surface vessels, Randall's plaques and non-obstructing stones, pelvic organ prolapse, asymptomatic vaginal atrophy, interstitial cystitis) and a subsequent UA shows a persistent, stable degree of MH, the Panel recommends SDM regarding whether to proceed with further repeat evaluation. Factors that may be considered are time since the initial (or prior) negative evaluation, presence of other risk factors, and overall risk stratification.

Changes in a patient's clinical status require careful consideration. Specifically, given the associations noted between the presence of GH, higher degrees of MH, and new or worsening urologic symptoms with the diagnosis of malignancy or clinically significant benign conditions, presentation with any of these should merit further evaluation.[6,8,42] Nevertheless, the low overall risk of malignancy in this population must again be acknowledged; therefore, a uniform approach to investigation in this setting cannot be mandated.

Ultimately, clinicians' judgement and patients' preferences are critical in the SDM process regarding whether to repeat the UA in the future or to release the patient from care.

FUTURE DIRECTIONS

The Panel recognizes the lack of high-level supporting evidence for many of the Guideline Statements and acknowledges several existing knowledge gaps that represent opportunities for future investigation to meaningfully enhance care.

Recent validation studies demonstrated the 2020 risk stratification system separated MH patients into clinically meaningful categories justifying the graduated intensity of evaluation. However, both retrospective and prospective studies utilizing the 2020 stratification system still result in most patients being classified as high-risk (>75%). While

this revised Guideline modifies the existing risk stratification, future work could include incorporation of nomograms or machine learning algorithms (with or without UBTMs) for more personalized risk assessment.

In addition to evaluating practice patterns regarding asymptomatic MH diagnosis and referral, better understanding of how clinicians diagnose and define MH is needed. For example, new automated instruments based either on flow cytometry or digitized microscopy are increasingly utilized to perform UA.[43] These machines may not correlate directly with traditional urine microscopy; thus, it will be important to determine if the threshold of 3 RBC/HPF used in the Guideline will be an equivalent predictor of risk when these new technologies are used in evaluation.

The utility of UBTMs in the evaluation of patients with MH is evolving. The appropriate incorporation of UBTM/cytology in the evaluation of MH is reliant on accurate risk stratification. Effort and education will need to be undertaken to ensure UBTM/cytology is limited to use in appropriate populations per current Guideline recommendations as a tool to reduce the use of cystoscopy during MH evaluation. Similarly, optimizing follow-up in patients with negative marker testing will be valuable. The necessity of such repeated evaluation should be evaluated as well as the optimal timing and should be a key endpoint for designing prospective marker-based trials.

This revised Guideline includes recent data demonstrating the low risk of diagnosis of a subsequent malignancy among patients with MH who have a negative evaluation, even among those with persistent (stable) MH. Many patients with MH will have persistent findings of microscopic blood—likely due to benign causes that may or may not be recognized—and depending on local practice patterns, may be a risk for persistent re-referral for evaluation. Strategies to mitigate this may be needed in the future.

MH is a highly prevalent condition, impacting a large population whose evaluation is managed by a wide variety of practitioners. The impact of this Guideline on frequency, intensity, yield of evaluation will need to be studied to determine the impact of the updated recommendations on public health and to inform the next Guideline update.

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