Microhematuria: AUA/SUFU Guideline

Unabridged version of this Guideline [pdf]
Algorithm associated with this Guideline [pdf]

Panel Members

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Executive Summary

Purpose

The purpose of this guideline is to provide a clinical framework for the diagnosis, evaluation, and follow-up of microhematuria (MH).

Methodology

OVID was used to systematically search MEDLINE and EMBASE databases for articles evaluating hematuria using criteria determined by the expert panel. The initial draft evidence report included evidence published from January 2010 through February 2019. A second search conducted to update the report included studies published up to December 2019. Five systematic reviews and 91 primary literature studies met the study selection criteria and were chosen to form the evidence base. These publications were used to create the majority of the clinical framework. When sufficient evidence existed, the body of evidence for a particular modality was assigned a strength rating of A (high), B (moderate), or C (low); and evidence-based statements of Strong, Moderate, or Conditional Recommendation were developed. Additional information is provided as Clinical Principles and Expert Opinions when insufficient evidence existed. See text and algorithm for definitions and detailed diagnostic, evaluation, and follow-up information.

Guideline Statements

Diagnosis and Definition of Microhematuria

1. Clinicians should define microhematuria as ≥3 red blood cells per high-power field on microscopic evaluation of a single, properly collected urine specimen. (Strong Recommendation; Evidence Level: Grade C)

2. Clinicians should not define microhematuria by positive dipstick testing alone. A positive urine dipstick test (trace blood or greater) should prompt formal microscopic evaluation of the urine. (Strong Recommendation; Evidence Level: Grade C)

Initial Evaluation

3. In patients with microhematuria, clinicians should perform a history and physical examination to assess risk factors for genitourinary malignancy, medical renal disease, gynecologic and non-malignant genitourinary causes of microhematuria. (Clinical Principle)

4. Clinicians should perform the same evaluation of patients with microhematuria who are taking antiplatelet agents or anticoagulants (regardless of the type or level of therapy) as patients not on these agents. (Strong Recommendation; Evidence Level: Grade C)

5. In patients with findings suggestive of a gynecologic or non-malignant urologic etiology, clinicians should evaluate the patients with appropriate physical examination techniques and tests to identify such an etiology. (Clinical Principle)

6. In patients diagnosed with gynecologic or non-malignant genitourinary sources of microhematuria, clinicians should repeat urinalysis following resolution of the gynecologic or non-malignant genitourinary cause. If microhematuria persists or the etiology cannot be identified, clinicians should perform risk-based urologic evaluation. (Clinical Principle)

7. In patients with hematuria attributed to a urinary tract infection, clinicians should obtain a urinalysis with microscopic evaluation following treatment to ensure resolution of the hematuria. (Strong Recommendation; Evidence Level: Grade C)

8. Clinicians should refer patients with microhematuria for nephrologic evaluation if medical renal disease is suspected. However, risk-based urologic evaluation should still be performed. (Clinical Principle)

Risk Stratification

9. Following initial evaluation, clinicians should categorize patients presenting with microhematuria as low-, intermediate-, or high-risk for genitourinary malignancy based on the accompanying tables (Tables 3 and 4). (Strong Recommendation; Evidence Level: Grade C)

Urinary Tract Evaluation

Low-Risk

10. In low-risk patients with microhematuria, clinicians should engage patients in shared decision-making to decide between repeating urinalysis within six months or proceeding with cystoscopy and renal ultrasound. (Moderate Recommendation; Evidence Level: Grade C)

Initially Low-Risk with Hematuria on Repeat Urinalysis

11. Low-risk patients who initially elected not to undergo cystoscopy or upper tract imaging and who are found to have microhematuria on repeat urine testing should be reclassified as intermediate- or high-risk. In such patients, clinicians should perform cystoscopy and upper tract imaging in accordance with recommendations for these risk strata (Strong Recommendation; Evidence Level: Grade C)

Intermediate-Risk

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

High-Risk

13. Clinicians should perform cystoscopy and axial upper tract imaging in patients with microhematuria categorized as high-risk for malignancy. (Strong Recommendation; Evidence Level: Grade C)

Options for Upper Tract Imaging in High-Risk Patient:

a. If there are no contraindications to its use, clinicians should perform multiphasic CT urography (including imaging of the urothelium). (Moderate Recommendation; Evidence Level: Grade C)

b. If there are contraindications to multiphasic CT urography, clinicians may utilize MR urography. (Moderate Recommendation; Evidence Level: Grade C)

c. If there are contraindications to multiphasic CT urography and MR urography, clinicians may utilize retrograde pyelography in conjunction with non-contrast axial imaging or renal ultrasound. (Expert Opinion)

14. Clinicians should perform white light cystoscopy in patients undergoing evaluation of the bladder for microhematuria. (Moderate Recommendation; Evidence Level: Grade C)

15. In patients with persistent or recurrent microhematuria previously evaluated with renal ultrasound, clinicians may perform additional imaging of the urinary tract. (Conditional Recommendation; Evidence Level: Grade C)

16. In patients with microhematuria who have a family history of renal cell carcinoma or a known genetic renal tumor syndrome, clinicians should perform upper tract imaging regardless of risk category. (Expert Opinion)

Urinary Markers

17. Clinicians should not use urine cytology or urine-based tumor markers in the initial evaluation of patients with microhematuria. (Strong Recommendation; Evidence Level: Grade C)

18. Clinicians may obtain urine cytology for patients with persistent microhematuria after a negative workup who have irritative voiding symptoms or risk factors for carcinoma in situ. (Expert Opinion)

Follow-Up

19. In patients with a negative hematuria evaluation, clinicians may obtain a repeat urinalysis within 12 months. (Conditional Recommendation; Evidence Level: Grade C)

20. For patients with a prior negative hematuria evaluation and subsequent negative urinalysis, clinicians may discontinue further evaluation for microhematuria. (Conditional Recommendation; Evidence Level: Grade C)

21. For patients with a prior negative hematuria evaluation who have persistent or recurrent microhematuria at the time of repeat urinalysis, clinicians should engage in shared decision-making regarding need for additional evaluation. (Expert Opinion)

22. For patients with a prior negative hematuria evaluation who develop gross hematuria, significant increase in degree of microhematuria, or new urologic symptoms, clinicians should initiate further evaluation. (Moderate Recommendation; Evidence Level: Grade C)

Introduction

Prevalence

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%-31.1% depending on the specific population evaluated. [2]

Etiologies

Urologic etiologies for hematuria include malignancy, infection, inflammation, calculus disease, benign prostatic hyperplasia (BPH), and congenital or acquired anatomic abnormalities. [3] Hematuria may also be confused with gynecological sources of bleeding, myoglobinuria, or pigmentation of the urine from the ingestion of certain foods and drugs. When considering the risk of malignancy in patients with hematuria, a recent prospective observational study of over 3,500 patients referred for evaluation of hematuria noted a 10.0% rate of urinary tract cancer: 13.2% for patients with gross hematuria (GH) and 3.1% among patients with MH. [4] Similarly, aggregate data from 17 prior MH screening studies published between 1980 to 2011 identified in the 2012 AUA Guideline reported a urinary tract malignancy rate of 2.6% (range 0% to 25.8%), the vast majority of which were bladder cancers. [2] Eleven more contemporary studies enrolling MH patients in the current evidence base dating from 2010 to 2019 reported an aggregate urinary tract malignancy rate of 1% (range 0.3% to 6.25%), which varied according to the presence or absence of risk factors for malignancy. [5-15]

Diagnostic Evaluation of Microhematuria

While most experts agree that patients with 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. [16,17] The 2012 AUA Guideline recommended computed tomography (CT) urography and cystoscopy in all patients over 35 years of age with MH, and were largely crafted without regard to patients' risk of malignancy. Indeed, the principal goal of the 2012 Guideline was to minimize the likelihood of missing a malignancy diagnosis. [2] Consistent with this intention, a theoretical simulation model determined that this evaluation would miss detection of the fewest number of cancers relative to other existing guidelines. [17] Nevertheless, this approach has attendant patient risk (e.g., discomfort and risk of infection with cystoscopy, risk of contrast reactions, potential for radiation-induced cancers attributed to CT, detection of false-positive findings leading to further investigation),17 and an incremental healthcare cost approximately twice that of guidelines from other organizations. [17,18] In light of the overall low rate of cancers detected among patients with MH, the implications of diagnostic studies must be considered both at the patient and health system level.

At the same time, practice-pattern assessments have demonstrated significant inconsistencies in the evaluation of patients presenting with hematuria. For example, one study found that less than 50% of patients with hematuria diagnosed in a primary care setting were subsequently referred for urologic evaluation. [19] Moreover, in a series of patients presenting with hematuria who had known risk factors for bladder cancer, only 23% received any type of imaging, and only 13% underwent cystoscopy. [10] The underuse of cystoscopy, and the tendency to use only imaging for evaluation, is particularly concerning when one considers that the vast majority of cancers diagnosed among persons with hematuria are bladder cancers, optimally detected with cystoscopy. 7,8,10,13-15,20-23

Women with hematuria have been especially prone to delays in evaluation, often due to practitioners ascribing hematuria to a urinary tract infection (UTI) or gynecologic source, resulting in inadequate evaluation and delay in cancer diagnosis. [19,24] Similarly, studies have found that African American patients are less likely than Caucasian counterparts to undergo any aspect of hematuria evaluation, including urology referral, cystoscopy, and

imaging. [25] In turn, despite having a lower incidence of bladder cancer than men, women diagnosed with bladder cancer have a lower 5-year survival than men (73.3% versus 78.2%), which may be in part attributable to delay in diagnosis leading to higher stage disease at diagnosis. [26] Likewise, racial differences in five-year survival and stage at diagnosis for urothelial cancer have also been noted, with evidence demonstrating lower rates of referral to urology and lower use of imaging in women and African Americans with hematuria compared to men and whites, which may explain some of this variation in disease burden at diagnosis and in survival. [25,27,28] 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. [29]

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. Furthermore, since deciding how aggressively to pursue an etiology for MH involves tradeoffs at the individual level (risk of malignancy versus harms of evaluation), it is necessary for the clinician and patient to engage in shared decision-making, particularly in situations where the ratio of benefits to harms is uncertain, equivalent or “preference sensitive” (e.g., dependent on the value that an individual patient may place on them). [30]

This 2020 AUA Guideline for MH was developed with these goals in mind. The aim is to provide an individualized approach to hematuria evaluation based on the patient’s risk of harboring a urinary tract cancer and concordant with the patient’s values. In the process, it is recognized that tailoring the intensity of evaluation to patient risk, as opposed to recommending intensive evaluation for every patient irrespective of harms and costs, will inevitably introduce the potential for some missed cancers. Nonetheless, the proposed approach seeks to optimize the balance of detection and risk at both the patient and health system level. In addition, the Panel aims to put forth an actionable set of recommendations that will facilitate standardization in order to minimize unnecessary variations and the risk of under-evaluation and delayed diagnosis of important urologic conditions. The recommendations herein, based on analysis of the best available evidence, represent a patient-centered approach by maximizing the opportunities to diagnose important urologic conditions in a timely fashion, while avoiding unnecessary evaluations in low-risk patients.

Methodolgy

The systematic review utilized to inform this guideline was conducted by an independent methodological consultant. Determination of the guideline scope and review of the final systematic review to inform guideline statements was conducted in conjunction with the MH Panel.

Panel Formation

The Panel was created in 2018 by the American Urological Association Education and Research, Inc. (AUAER). This guideline was developed in collaboration with the Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU). The Practice Guidelines Committee (PGC) of the AUA selected the Panel Chairs who in turn appointed the additional panel members with specific expertise in this area in conjunction with SUFU. Additionally, the Panel included representation from the American College of Obstetricians and Gynecologists (ACOG) as well as a patient advocate. Funding of the Panel was provided by the AUA; panel members received no remuneration for their work.

Searches and Article Selection

A systematic review was conducted to inform on appropriate diagnosis, evaluation, and follow-up in patients with suspected and confirmed MH. The methodologist, in consultation with the expert panel, developed criteria for inclusion and exclusion of studies based on the Key Questions and the populations, interventions, comparators, and outcomes (PICO) of interest. OVID was used to systematically search MEDLINE and EMBASE databases for articles evaluating hematuria using the criteria determined by the expert panel. Five systematic reviews and 91 primary literature studies met the study selection criteria and were chosen to form the evidence base. Based on a low volume of studies identified enrolling solely MH patients, studies that enrolled a combination MH and GH population were included in the evidence base. Studies enrolling the two populations were described separately in text and tables.

Control articles, which were deemed important and relevant by the Panel, were compared with the draft literature search strategy output, and the final strategy was updated as necessary to capture all control articles. In addition to the MEDLINE and EMBASE databases searches, reference lists of included systematic reviews and primary literature were scanned for potentially useful studies.

All hits from the OVID literature search were input into reference management software (EndNote X7), where duplicate citations were removed. Abstracts were reviewed by the methodologist to determine if the study addressed the Key Questions and if the study met study design inclusion criteria. For all research questions, randomized controlled trials (RCTs), observational studies, and case-control studies were considered for inclusion in the evidence base. Studies had to enroll at least 30 patients per study arm. Case series, letters, editorials, *in vitro* studies, studies conducted in animal models, and studies not published in English were excluded from the evidence base.

Full-text review was conducted on studies that passed the abstract screening phase. Studies were compared to the predetermined PICO as outlined below. Nine panel members were paired with the methodologist and completed duplicate full-text study selection of 10% of studies undergoing full-text review. The dual-review trained the methodologist, who then completed full-time review of the remaining studies.

Population

- All adult (≥18 years) patients with suspected or confirmed MH
- Studies enrolling mixed population MH and GH patients were considered for inclusion
    1. Studies enrolling solely GH populations were excluded

Interventions

- Hematuria detection by urinalysis (UA) or dipstick
- Complete hematuria work-up components
- Risk factors for malignancy and/or mortality
- Imaging modalities
- Cystoscopy
- Urinary marker assays
- Patient engagement tools and decision aids

- Follow-up schedules in patients with initial negative hematuria evaluation

Comparators

- Any of the included interventions of interest when defined as the control group and compared to another intervention
    - It was anticipated that a majority of the identified studies would be single arm

Outcomes

- Critical outcomes
    - Hematuria detection concordance (UA versus dipstick)
    - Diagnostic yield, incorporating prevalence of malignant and/or benign diagnoses
    - Diagnostic test characteristics, including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and false positive rate
    - Risk stratification for urologic malignancy
    - Risk stratification system performance characteristics, including predictive ability, prognostic ability, number needed to screen
    - Rate of adverse events and number needed to harm
- Imporant outcomes
    - Disease specific sruvival rates
    - Diagnostic grade/stage of malignancy
    - Prevalence of risk factors in hematuria patients
    - Patient satisfaction
    - Quality of life

The initial draft evidence report included evidence published from January 2010 through February 2019. A second search was conducted to update the report to include studies published up to December 2019.

Data Abstraction

Data were extracted from all studies that passed full-text review by the methodologist. All extracted data were audited by an independent auditor.

Risk of Bias Assessment

Quality assessment for all retained studies was conducted. Using this method, studies deemed to be of low quality would not be excluded from the systematic review, but would be retained, and their methodological strengths and weaknesses discussed where relevant. To define an overall study quality rating for each included study, risk of bias as determined by validated study-type specific tools, was paired with additional important quality features. To evaluate the risk of bias within the identified studies, the Assessment of Multiple Systematic Reviews (AMSTAR) [31] tool was used for systematic reviews, the Cochrane Risk of Bias Tool [32] was used for randomized studies, and a Risk of Bias in Non-Randomized Studies – of

Intervention (ROBINS-I) [33] was used for observational studies. Additional important quality features, such as study design, comparison type, power of statistical analysis, and sources of funding were extracted for each study.

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) [34] system was used to determine the aggregate evidence quality for each guideline statement. GRADE defines a body of evidence in relation to how confident guideline developers can be that the estimate of effects as reported by that body of evidence is correct. Evidence is categorized as high, moderate, low, and very low; and assessment is based on the aggregate risk of bias for the evidence base plus limitations introduced as a consequence of inconsistency, indirectness, imprecision, and publication bias across the studies. [35] Additionally, certainty of evidence can be downgraded if confounding across the studies has resulted in the potential for the evidence base to overestimate the effect. Upgrading of evidence is possible if the body of evidence indicates a large effect or if confounding would suggest either spurious effects or would reduce the demonstrated effect.

Data Synthesis

One of the main objectives for the guideline is to establish a risk model to stratify patients based on their risk for underlying urologic malignancy. To this end, pooling of data was conducted in three areas using RevMan. [36] For studies that reported adjusted odds ratios (without raw data) for risk factors associated with malignancy, the odds ratios were pooled using a random-effects inverse-variance method. For studies that reported raw data on patient factors and their association with malignant diagnosis, unadjusted odds ratios were calculated and pooled using a random-effects Mantel-Haenszel method. Finally, prevalence of both malignant and benign diagnoses in relation to the type of hematuria work-up received by patients were calculated and pooled using a random-effects inverse-variance method. For all other areas, pooling was determined to be inappropriate based on heterogeneity of population, reference standard, or reported outcomes.

Determination of Evidence Strength

The AUA employs a three-tiered strength of evidence system to underpin evidence-based guideline statements. In short, high certainty by GRADE translates to AUA A-category strength of evidence, moderate to B, and both low and very low to C. (Table 1)

The AUA categorizes body of evidence strength as Grade A (well-conducted and highly-generalizable RCTs or exceptionally strong observational studies with consistent findings), Grade B (RCTs with some weaknesses of procedure or generalizability or moderately strong observational studies with consistent findings), or Grade C (RCTs with serious deficiencies of procedure or generalizability or extremely small sample sizes or observational studies that are inconsistent, have small sample sizes, or have other problems that potentially confound interpretation of data). By definition, Grade A evidence is evidence about which the Panel has a high level of certainty, Grade B evidence is evidence about which the Panel has a moderate level of certainty, and Grade C evidence is evidence about which the Panel has a low level of certainty. [37]

Table 1: Strength of Evidence Definitions

AUA Strength of Evidence Category	GRADE Certainty Rating	Definition
A	High	• Very confident that the true effect lies close to that of the estimate of the effect

Table 1: Strength of Evidence Definitions		
B	Moderate	•Moderatley confident in the effect estimate • The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
C	Low Very Low	• Confidence in the effect estimate is limited • The true effect may be substantially different from the estimate of the effect • Very little confidence in the effect estimate • The true effect is likely to be substantially different from the estimate of effect

AUA Nomenclature: Linking Statement Type to Evidence Strength

The AUA nomenclature system explicitly links statement type to body of evidence strength, level of certainty, magnitude of benefit or risk/burdens, and the Panel's judgment regarding the balance between benefits and risks/burdens (Table 2). Strong Recommendations are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken because net benefit or net harm is substantial. Moderate Recommendations are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken because net benefit or net harm is moderate. Conditional Recommendations are non-directive statements used when the evidence indicates that there is no apparent net benefit or harm, when benefits and harms are finely balanced, or when the balance between benefits and risks/burden is unclear. All three statement types may be supported by any body of evidence strength grade. Body of evidence strength Grade A in support of a Strong or Moderate Recommendation indicates that the statement can be applied to most patients in most circumstances and that future research is unlikely to change confidence. Body of evidence strength Grade B in support of a Strong or Moderate Recommendation indicates that the statement can be applied to most patients in most circumstances but that better evidence could change confidence. Body of evidence strength Grade C in support of a Strong or Moderate Recommendation indicates that the statement can be applied to most patients in most circumstances but that better evidence is likely to change confidence. Conditional Recommendations also can be supported by any evidence strength. When body of evidence strength is Grade A, the statement indicates that benefits and risks/burdens appear balanced, the best action depends on patient circumstances, and future research is unlikely to change confidence. When body of evidence strength Grade B is used, benefits and risks/burdens appear balanced, the best action also depends on individual patient circumstances and better evidence could change confidence. When body of evidence strength Grade C is used, there is uncertainty regarding the balance between benefits and risks/burdens; therefore, alternative strategies may be equally reasonable, and better evidence is likely to change confidence.

Where gaps in the evidence existed, the Panel provides guidance in the form of Clinical Principles or Expert Opinions with consensus achieved using a modified Delphi technique if differences of opinion emerged. [38] A Clinical Principle is a statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature. Expert Opinion refers to a statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there may or may not be evidence.

TABLE 2: AUA Nomenclature Linking Statement Type to Level of Certainty, Magnitude of Benefit or Risk/Burden, and Body of Evidence Strength

	Evidence Strength A (High Certainty)	Evidence Strength B (Moderate Certainty)	Evidence Strength C (Low Certainty)
Strong Recommendation (Net benefit or harm substantial)	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is substantial Applies to most patients in most circumstances and future research unlikely to change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is substantial Applies to most patients in most circumstances but better evidence could change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) appears substantial Applies to most patients in most circumstances but better evidence is likely to change confidence (rarely used to support a Strong Recommendation)
Moderate Recommendation (Net benefit or harm moderate)	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is moderate Applies to most patients in most circumstances and future research is unlikely to change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is moderate Applies to most patients in most circumstances but better evidence could change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) appears moderate Applies to most patients in most circumstances but better evidence is likely to change confidence
Conditional Recommendation (No apparent net benefit or harm)	Benefits = Risks/Burdens Best action depends on individual patient circumstances Future research unlikely to change confidence	Benefits = Risks/Burdens Best action appears to depend on individual patient circumstances Better evidence could change confidence	Balance between Benefits & Risks/Burdens unclear Alternative strategies may be equally reasonable Better evidence likely to change confidence
Clinical Principle	A statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature		
Expert Opinion	A statement, achieved by consensus of the Panel, that is based on members clinical training, experience, knowledge, and judgment for which there is no evidence		

Peer Review and Document Approval

An integral part of the guideline development process at the AUA is external peer review. The AUA conducted a thorough peer review process to ensure that the document was reviewed by experts in the diagnosis, evaluation, and follow-up of MH. In addition to reviewers from the AUA PGC, Science and Quality Council (SQC), and Board of Directors (BOD), the document was reviewed by representatives from SUFU and ACOG as well as external content experts. Additionally, a call for reviewers was placed on the AUA website from December 2-16, 2019 to allow any additional interested parties to request a copy of the document for review. The guideline was also sent to the Urology Care Foundation and representatives of the Bladder Cancer Advocacy Network (BCAN) to open the document further to the patient perspective. The draft guideline document was distributed to 115 peer reviewers. All peer review comments were blinded and sent to the Panel for review. In total, 66 reviewers provided comments, including 51 external reviewers. At the end of the peer

review process, a total of 443 comments were received. Following comment discussion, the Panel revised the draft as needed. Once finalized, the guideline was submitted for approval to the AUA PGC, SQC, and BOD as well as the governing body of SUFU for final approval.

Diagnosis and Definition of Microhematuria (MH)

Guideline Statement 1

1. Clinicians should define microhematuria as ≥3 red blood cells per high-power field on microscopic evaluation of a single, properly collected urine specimen. (Strong Recommendation; Evidence Level: Grade C)

Discussion

In order to inform clinicians of the degree of hematuria with sufficient detail to determine whether further evaluation is warranted, the Panel emphasizes the importance of laboratories reporting red blood cells per high-power field (RBC/HPF) quantitatively. Although various thresholds may be utilized, the Panel encourages the use of ≥3 RBC/HPF as a minimum reporting threshold, consistent with prior AUA guidelines as well as newer data subsequently highlighted. [2] While several automated methods for assessing hematuria, including the use of flow cytometry, have diffused into clinical practice, at present, there is insufficient evidence regarding the accuracy of these devices in comparison to microscopic evaluation. As such, microscopic quantification remains the referent standard for defining hematuria. [39]

In a recent study evaluating the correlation between degree of MH and malignancy among a group of over 46,000 patients, Matulewicz et al. noted that the highest sensitivity for detecting bladder cancer (0.73) and lowest negative likelihood ratio (0.40) existed at the threshold of ≥3 to 10 RBC/HPF. [5] By defining a low threshold for defining MH, the potential for inadvertently excluding patients at risk for harboring urologic malignancy was considered low. In particular, with the risk stratified evaluation approach outlined below, the Panel felt it was necessary to be inclusive at this definition stage whilst subsequent evaluation would be modulated by individual patient risk.

Meanwhile, the Panel noted limited new data since the previous iteration of the AUA Guideline regarding the role of single versus multiple UAs as part of the diagnostic evaluation. One retrospective MH cohort study reporting on the diagnostic yield of a single UA compared with multiple noted that the initial UA detected MH in 95% of the patients, while addition of the second and third UA detected the remaining 5%. [40] Given the intermittent nature of hematuria and the absence of robust new evidence to alternatively inform practice, the Panel maintained that only a single UA with ≥3 RBC/HPF is necessary to establish the presence of MH. The Panel does recognize that although a positive dipstick does not warrant MH evaluation, data exist correlating the extent of dipstick positivity with the likelihood of identifying a greater number of RBC/HPF on UA. [5,41] Therefore, in patients with a greater degree of blood on urine dipstick but a negative UA, clinicians may consider follow-up with repeat UA, including patient risk and preference in the decision process.

Proper Sample Collection

For most initial evaluations, a random midstream clean-catch collection is sufficient. Patients should be instructed to discard the initial 10 mL of voided urine into the toilet in order to collect the midstream void. If a significant number of squamous cells are present in the sample, then contamination is possible and a repeat specimen collection or catheterization should be considered. Providing basic instructions to patients on proper sample collection, verbally, in writing, or on posted signs, could minimize contaminated or faulty samples.

Male patients: Midstream voided specimens are adequate unless the patient is unable to void. The specimen can be collected into the sterile specimen cup after gently cleaning the urethral meatus with a sterilization towelette. In uncircumcised men, it is important to retract the foreskin to avoid contamination.

Female patients: A voided midstream specimen should be the primary method unless there are circumstances such as known problems with repeated specimen contamination or a history of difficulty voiding. The patient should be instructed to spread the labia adequately to allow for cleansing of the urethral meatus with a sterilization towelette and to avoid introital contamination.

In some patients, catheterization may be necessary in order to obtain an appropriate specimen. This subgroup includes obese female patients and patients with a non-intact urinary tract, a Foley catheter, a suprapubic catheter, or who use intermittent catheterization. Women with concurrent menstruation should be reevaluated after its cessation or should undergo catheterization to determine if the blood is in fact present in the urine or is only noted as a result of vaginal contamination.

Specimen: The specimen container should be labeled per institutional protocol and analyzed within standard laboratory regulations. Method of collection, date, and time should be included in the labeling.

Analytic Technique

Analytic techniques vary, with some now using flow cytometry rather than microscopy. For more detail, one can consult with the local laboratory director.

Urine specimens collected immediately after prolonged recumbency (first void in morning) or the first voiding after vigorous physical or sexual activity should not be examined to assess for microhematuria. [42,43] It should also be remembered that in dilute urine, usually below an osmolality of 308 mOsm, most RBCs lyse; therefore, the number of RBCs per 400x magnification may be artificially reduced. [44]

The Panel emphasizes that a positive dipstick merits microscopic examination of the urinary sediment as described, but does not warrant full evaluation unless microscopic evaluation confirms ≥3 RBC/HPF. If this is not the case but the clinician is suspicious that the findings could reflect true MH, then repeat microscopic testing may be reasonable after assessing patient risk and preference.

Guideline Statement 2

2. Clinicians should not define microhematuria by positive dipstick testing alone. A positive urine dipstick test (trace blood or greater) should prompt formal microscopic evaluation of the urine. (Strong Recommendation; Evidence Level: Grade C)

Discussion

In order to inform clinicians of the degree of hematuria with sufficient detail to determine whether further evaluation is warranted, the Panel emphasizes the importance of laboratories reporting red blood cells per high-power field (RBC/HPF) quantitatively. Although various thresholds may be utilized, the Panel encourages the use of ≥3 RBC/HPF as a minimum reporting threshold, consistent with prior AUA guidelines as well as newer data subsequently highlighted. [2] While several automated methods for assessing hematuria, including the use of flow cytometry, have diffused into clinical practice, at present, there is insufficient evidence regarding the accuracy of these devices in comparison to microscopic evaluation. As such, microscopic quantification remains the referent standard for defining hematuria. [39]

In a recent study evaluating the correlation between degree of MH and malignancy among a group of over 46,000 patients, Matulewicz et al. noted that the highest sensitivity for detecting bladder cancer (0.73) and lowest negative likelihood ratio (0.40) existed at the threshold of ≥3 to 10 RBC/HPF. [5] By defining a low threshold for defining MH, the potential for inadvertently excluding patients at risk for harboring urologic malignancy was considered low. In particular, with the risk stratified evaluation approach outlined below, the Panel felt it was necessary to be inclusive at this definition stage whilst subsequent evaluation would be modulated by individual patient risk.

Meanwhile, the Panel noted limited new data since the previous iteration of the AUA Guideline regarding the role of single versus multiple UAs as part of the diagnostic evaluation. One retrospective MH cohort study reporting on the diagnostic yield of a single UA compared with multiple noted that the initial UA detected MH in 95% of the patients, while addition of the second and third UA detected the remaining 5%. [40] Given the intermittent nature of hematuria and the absence of robust new evidence to alternatively inform practice, the Panel maintained that only a single UA with ≥3 RBC/HPF is necessary to establish the presence of MH. The Panel does recognize that although a positive dipstick does not warrant MH evaluation, data exist correlating the extent of dipstick positivity with the likelihood of identifying a greater number of RBC/HPF on UA. [5,41] Therefore, in patients with a greater degree of blood on urine dipstick but a negative UA, clinicians may consider follow-up with repeat UA, including patient risk and preference in the decision process.

Proper Sample Collection

For most initial evaluations, a random midstream clean-catch collection is sufficient. Patients should be instructed to discard the initial 10 mL of voided urine into the toilet in order to collect the midstream void. If a significant number of squamous cells are present in the sample, then contamination is possible and a repeat specimen collection or catheterization should be considered. Providing basic instructions to patients on proper sample collection, verbally, in writing, or on posted signs, could minimize contaminated or faulty samples.

Male patients: Midstream voided specimens are adequate unless the patient is unable to void. The specimen can be collected into the sterile specimen cup after gently cleaning the urethral meatus with a sterilization towelette. In uncircumcised men, it is important to retract the foreskin to avoid contamination.

Female patients: A voided midstream specimen should be the primary method unless there are circumstances such as known problems with repeated specimen contamination or a history of difficulty voiding. The patient should be instructed to spread the labia adequately to allow for cleansing of the urethral meatus with a sterilization towelette and to avoid introital contamination.

In some patients, catheterization may be necessary in order to obtain an appropriate specimen. This subgroup includes obese female patients and patients with a non-intact urinary tract, a Foley catheter, a suprapubic catheter, or who use intermittent catheterization. Women with concurrent menstruation should be reevaluated after its cessation or should undergo catheterization to determine if the blood is in fact present in the urine or is only noted as a result of vaginal contamination.

Specimen: The specimen container should be labeled per institutional protocol and analyzed within standard laboratory regulations. Method of collection, date, and time should be included in the labeling.

Analytic Technique

Analytic techniques vary, with some now using flow cytometry rather than microscopy. For more detail, one can consult with the local laboratory director.

Urine specimens collected immediately after prolonged recumbency (first void in morning) or the first voiding after vigorous physical or sexual activity should not be examined to assess for microhematuria. [42,43] It should also be remembered that in dilute urine, usually below an osmolality of 308 mOsm, most RBCs lyse; therefore, the number of RBCs per 400x magnification may be artificially reduced. [44]

The Panel emphasizes that a positive dipstick merits microscopic examination of the urinary sediment as described, but does not warrant full evaluation unless microscopic evaluation confirms ≥3 RBC/HPF. If this is not the case but the clinician is suspicious that the findings could reflect true MH, then repeat microscopic testing may be reasonable after assessing patient risk and preference.

Initial Evaluation

Guideline Statement 3

3. In patients with microhematuria, clinicians should perform a history and physical examination to assess risk factors for genitourinary malignancy, medical renal disease, gynecologic and non-malignant genitourinary causes of microhematuria. (Clinical Principle)

Discussion

A detailed history and physical examination should be performed in patients who are confirmed to have MH as defined in Statement 1. 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 (Table 3), with specific emphasis on assessing for smoking history, family history of urologic malignancies, and genetic or other risk factors for bladder or urothelial cancer, such as environmental/occupational exposures. Physical examination should include measurement of blood pressure and a genitourinary examination as dictated by the

clinical history. For example, in women, examination of the external genitalia, introitus, and periurethral tissue may identify urethral pathology or other gynecologic pathology to explain the noted MH.

Table 3: Urothelial Cancer Risk Factors

Risk Factors Included in AUA Microhematuria Risk Stratification System	Additional Urothelial Cancer Risk Factors* [6,14,47-51]
Age	Irritative lower urinary tract symptoms
Male sex	Prior pelvic radiation therapy
Smoking use	Prior cyclophosphamide/ifosfamide chemotherapy
Degree of microhematuria	Family history of urothelial cancer or Lynch Syndrome
Persistence of microhematuria	Occupational exposures to benzene chemicals or aromatic amines (e.g., rubber, petrochemicals, dyes)
History of gross hematuria	Chronic indwelling foreign body in the urinary tract

*The Panel recognizes that this list is not exhaustive.

Clinicians should also understand that the differential diagnosis for MH is broad, including a number of benign conditions (e.g., benign prostatic enlargement, nephrolithiasis, urethral strictures and diverticula, exposure to trauma, or recent urological procedures/catheterization), some of which in turn will merit treatment. Thus, the MH patient should be queried regarding these potential causes. For example, rates of calculus disease in MH patients range from 1.0% [12] to 20.0%, [52] with most studies reporting calculus disease rates above 5.0%; [7,9 ,11,21-23,53,54] rates of benign prostatic enlargement range from 3.9% [54] to 52.7%; [52] and urethral stricture rates of 1% or less were reported in two studies of MH patients. [10,15]

A retrospective study [14] of 1,049 patients undergoing evaluation for MH is further illustrative of the diverse etiologies. Only 12 (1.1%) patients were diagnosed with a urologic malignancy, including 1 upper tract urothelial tumor, 5 renal masses (3 small), and 6 bladder tumors, of which 2 were high grade and 4 were low grade. Conversely, 620 patients had a negative work-up, while 417 patients had benign diagnoses, including 119 with stones and 298 with other benign diagnoses including urethral strictures, BPH, and renal cysts.

Given this broad differential diagnosis that includes non-malignant urologic etiologies that may nevertheless require intervention, clinicians should perform a probative history and physical examination. As gynecological bleeding may be confused with MH, a menstrual and gynecological history should be obtained, and a catheterized UA may be helpful to confirm MH. A more extensive gynecologic history and pelvic examination should be performed by a clinician capable of assessing for gynecologic conditions when indicated by the gynecologic history. Symptoms and signs of UTI, such as fever and dysuria, should be elicited. Patients should be asked about the presence of flank pain, which may herald a urinary tract stone, and obstructive urinary symptoms, which may signal the presence of prostatic hypertrophy or urethral stricture. Hypertension, history of kidney disease, dysmorphic RBCs, and proteinuria may

indicate glomerular disease. Thus, the initial evaluation should also include measurement of serum creatinine and an estimate of glomerular filtration rate, both to identify kidney disease and to guide the choice of imaging modality, should that be deemed necessary based on patient risk (see below). Patients should also be asked about recent perineal trauma or genitourinary instrumentation.

Guideline Statement 4

4. Clinicians should perform the same evaluation of patients with microhematuria who are taking antiplatelet agents or anticoagulants (regardless of the type or level of therapy) as patients not on these agents. (Strong Recommendation; Evidence Level: Grade C)

Discussion

Patients on anticoagulants should be assessed in the same fashion as patients who are not anticoagulated regardless of type or level of therapy (i.e., aspirin, warfarin, or other antiplatelet or antithrombotic agents) because these patients have a risk of malignancy that is similar to other populations. [55-57] Although few studies have specifically stratified cancer detection rates according to anticoagulation status, several prior studies of MH patients included a substantive representation of patients who were receiving antiplatelet or anticoagulant therapy. For example, Koo et al. demonstrated a 5.8% detection of bladder cancer in 411 consecutive patients with MH, of whom 15.3% were anticoagulated. [21] Further, a series of patients with GH on either anticoagulant or aspirin therapy found tumors in a quarter of patients, and other treatable findings in approximately half the cohort. [58]

Meanwhile, a population-based cohort study from Ontario reported that patients exposed to antithrombotic medications were significantly more likely to be diagnosed with bladder cancer within six months than patients not exposed to these medications, [59] suggesting the potential that such anticoagulation may unmask bleeding from an underlying malignancy. Therefore, clinicians should not dismiss MH in patients on anticoagulants or antiplatelet agents; rather, they should undergo risk-based evaluation in the same fashion as other patients not on these agents.

Guideline Statement 5

5. In patients with findings suggestive of a gynecologic or non-malignant urologic etiology, clinicians should evaluate the patients with appropriate physical examination techniques and tests to identify such an etiology. (Clinical Principle)

Guideline Statement 6

6. In patients diagnosed with gynecologic or non-malignant genitourinary sources of microhematuria, clinicians should repeat urinalysis following resolution of the gynecologic or non-malignant genitourinary cause. If microhematuria persists or the etiology cannot be identified, clinicians should perform risk-based urologic evaluation. (Clinical Principle)

Guideline Statement 7

7. In patients with hematuria attributed to a urinary tract infection, clinicians should obtain a urinalysis with microscopic evaluation following treatment to ensure resolution of the hematuria. (Strong Recommendation; Evidence Level: Grade C)

Discussion

If the history and physical examination suggest the presence of a gynecologic or non-malignant source of MH, the clinician should perform a directed evaluation to rule in or rule out such an etiology. For example, women with a suspected gynecologic source of MH should be evaluated by a clinician capable of assessing for and treating gynecologic disorders, whether that is a urologist with such expertise, a gynecologist, an experienced primary care provider, or other experienced clinician. A catheterized UA may be helpful to confirm MH in patients when findings suggest a potential gynecologic source of MH. Patients suspected to have UTI should undergo urine culture and, if necessary, antibiotic treatment. Similarly, patients suspected of having urolithiasis, urethral stricture disease, urethral diverticulum, or other non-malignant sources of MH should be evaluated appropriately to rule in or rule out these causes.

Following a directed evaluation, if no etiology is identified, further risk-based urologic evaluation should be undertaken. In patients who are found to have a non-malignant source of hematuria, the non-malignant diagnosis should be treated appropriately and then the urine should be re-tested for presence of MH. Persistent MH after resolution of the non-malignant cause should prompt risk-based urologic evaluation. In particular, those patients suspected to have a UTI as the etiology of MH should be treated for the UTI and then should undergo repeat UA to confirm resolution of the MH. If the MH does not resolve following treatment of the UTI, a risk-based urologic evaluation should be performed. The Panel acknowledges that there are some non-malignant urologic and gynecologic conditions, such as BPH, non-obstructing nephrolithiasis, vaginal atrophy or pelvic organ prolapse, which will not merit treatment or in which the MH may not resolve completely even with appropriate management. In these cases, clinicians must use careful judgment and shared decision-making to decide whether to pursue MH evaluation. Attention to the patient's risk factors for urologic malignancy should inform these decisions.

The risks of under-evaluating women with MH, and specifically the frequent misattribution of MH to UTI without sufficient evidence to support the diagnosis, or sufficient follow-up to confirm resolution of MH after treatment of UTI, merit mention. Cohn et al. evaluated gender disparities in the diagnosis of bladder cancer following presentation with hematuria and found that women with bladder cancer had a higher mortality relative to incidence compared to men. [24] Women who present with irritative symptoms are frequently treated empirically with antibiotics for a presumed UTI, as supported by practice-pattern data demonstrating that women have more urinalyses and cultures submitted compared to men, and are more often treated with multiple rounds of antibiotics.24 Indeed, Cohn et al. found the mean number of urinalyses sent for men versus women were 1.19 (95%CI: 1.16 to 1.45) and 1.39 (95%CI: 1.16 to 1.23), respectively ($p<0.001$). [24] Similarly, a mean of 0.53 (95%CI: 0.51 to 0.55) and 0.83 (95%CI: 0.78 to 0.88) urine cultures were sent in men and women with hematuria, respectively ($p<0.001$). [24] When reviewing antibiotic treatment, 8.7% of women were treated with >3 courses of antibiotics compared to 5.2% of men ($p<0.001$). [24] Moreover, a separate investigation found that in the year prior to bladder cancer diagnosis, symptomatic treatment without evaluation was given to 47% of women, with nearly 16% receiving ≥3 treatments for UTI. [60] In addition, studies have demonstrated sex-based disparities in evaluation of hematuria as well. In one such series, women with hematuria were significantly less likely than men to undergo cystoscopy (OR 0.48;

95%CI 0.37 to 0.62; p<0.001), upper tract imaging (OR 0.47; 95%CI 0.36 to 0.61; p<0.001), and complete evaluation with both cystoscopy with upper tract imaging (OR 0.31; 95%CI 0.24 to 0.45; p<0.001). The sequelae of such a delay and of under-evaluation may be the longer reported time from presentation with hematuria to diagnosis of bladder cancer noted in women. [61]

In light of these noted practice patterns, the Panel believes it important to emphasize the need for follow-up UA following resolution of a presumed gynecologic or non-malignant urologic cause of MH to confirm resolution of the MH. While there is no evidence-based interval for repeating the UA, MH may not resolve for several weeks to a few months following treatment of a gynecologic or non-malignant cause of MH, or treatment of a UTI. As such, the panel concludes that waiting at least three weeks after resolution of the non-malignant etiology and no more than three months would be appropriate. If the MH persists at that time, a risk-based urologic evaluation should be performed

Guideline Statement 8

8. Clinicians should refer patients with microhematuria for nephrologic evaluation if medical renal disease is suspected. However, risk-based urologic evaluation should still be performed. (Clinical Principle)

Discussion

Patients with proteinuria, dysmorphic RBCs, cellular casts, or renal insufficiency may have medical renal disease, which can cause hematuria. Therefore, patients with these features should be referred to a nephrologist. While evaluation for medical renal disease should be performed, this does not preclude the need to proceed with risk-based urologic evaluation. In fact, several studies have suggested an increased risk of renal cancer in patients with impaired renal function. For example, in a retrospective cohort study of 1,190,538 adult patients in a single healthcare system, Lowrance et al. [62] demonstrated an increased risk in the development of renal and urothelial cancers associated with lower eGFR. For renal cancers, the risk increased with decrease in eGFR (adjusted HR 1.39; 95%CI 1.22 to 1.58 for eGFR=45-59; HR 1.81; 95%CI 1.51 to 2.17 for eGFR=30-44; HR 2.28; 95%CI 1.78 to 2.92 for eGFR<30). The increased risk of urothelial cancer was noted in patients with an eGFR <30.

Risk Stratification

Guideline Statement 9

9. Following initial evaluation, clinicians should categorize patients presenting with microhematuria as low-, intermediate-, or high-risk for genitourinary malignancy based on the accompanying tables (Tables 3 and 4). (Strong Recommendation; Evidence Level: Grade C)

Discussion

Patient-centered approach to diagnostic evaluation

The Panel recognizes that patients presenting with hematuria represent a heterogeneous population with a broad spectrum of risk for underlying malignant causes based on clinical and demographic features. Prior recommendations for diagnostic testing strategies have primarily focused on test accuracy, [63] particularly sensitivity and specificity, with estimates pooled across the continuum of risk factors. It should be noted that much of the available literature in this context aggregates outcomes of patients across the risk spectrum; for instance, those presenting with MH and GH. As such, systematic aggregation of evidence in this context may lead to the conclusion that a diagnostic testing strategy provides equal benefit to everyone who receives it, when in reality benefits and harms more often vary from patient to patient. The Panel recognizes that the actual performance of a testing strategy in clinical practice is a complex and dynamic function of pretest and posttest probability for the outcome(s) of interest. Put another way, the balance of benefits and harms for a given approach to evaluation varies in a predictable way across groups of similar individuals. Within this framework, expected performance of a testing strategy in a given clinical encounter implies knowledge of its performance within a particular subgroup, not the weighted average over broad and heterogeneous populations. [64] Recognizing patient-specific characteristics modifying the risk of underlying malignant causes, risk stratification in hematuria evaluation supports more personalized diagnostic testing strategies as opposed to a “one-size-fits-all” approach.

Risk Stratification

Several risk stratification models have been described from cohorts of patients undergoing evaluation of hematuria. One, the Hematuria Risk Index (HRI), was developed based on a multivariable analysis of 4,414 patients, assigning points based on the strength of association between risk factors and malignancy identified on evaluation in regression analyses. [7] Factors included in this model were a patient’s history of GH, age ≥50 years, smoking history, male sex, and the presence of >25 RBC/HPF on UA. On the basis of these factors, patients were categorized as low-, moderate-, or high-risk, with an associated risk of underlying malignancy of 0.2%, 1.6%, and 11.1%, respectively. In this population, 32.3% of patients were low-risk, 53.3% intermediate-risk, and 14.3% high-risk. The HRI was subsequently validated in a cohort of 3,573 women undergoing evaluation of hematuria, with urologic cancer identified in 0.5% of low-risk, 1.3% of moderate-risk, and 10.8% of high-risk patients. Meanwhile, a separate model, the Haematuria Cancer Risk Score (HCRS) was developed based on a multivariable analysis of 3,539 patients evaluated in UK hospitals and externally validated in a cohort of 656 Swiss patients. [65] Patient age, sex, type of hematuria, and smoking history (former versus current) were identified as independent predictors of malignancy, and weights were assigned to each based on coefficients from the regression analysis. [65] The HCRS detected 11.4% more cancers that would have been missed by UK National Institute for Health and Clinical Excellence Guidelines, while the specificity of HCRS was calculated to be 30.5%.

The Panel acknowledges that Grade A evidence does not support stratification as affecting clinical outcomes or survival. Nevertheless, the Panel believes that there is value to creating categories to broadly estimate the likelihood of an underlying malignant diagnosis in order to facilitate patient-centered testing strategies across the heterogeneous population with hematuria. The Panel set out to create such a system,

with categories summarized as ‘low-,’ ‘intermediate-,’ and ‘high-’ risk for a malignant diagnosis associated with hematuria (Table 4). This risk grouping system is intended as a simple tool for application in clinical practice as a general framework to support patient counseling and diagnostic testing decisions. While there are similarities between the current risk categories outlined in the Guideline and published risk score models summarized previously, it should be acknowledged that these risk categories are not based on meta-analyses or original studies, and instead represent the Panel’s consensus based on a review of available data on risk factors for urinary tract malignancy.

Table 4: AUA Microhematuria Risk Stratification System

Low (patient meets all criteria)	Intermediate (patients meets any one of these criteria)	High (patients meets any one of these criteria)
• Women age <50 years; Men age <40 years • Never smoker or <10 pack years • 3-10 RBC/HPF on a single urinalysis • No risk factors for urothelial cancer (see Table 3)	• Women age 50-59 years; Men age 40-59 years • 10-30 pack years • 11-25 RBC/HPF on a single urinalysis • Low-risk patient with no prior evaluation and 3-10 RBC/HPF on repeat urinalysis • Additional Risk factors for urothelial cancer (see Table 3)	• Women or Men age ≥60 years • >30 pack years • >25 RBC/HPF on a single urinalysis • History of gross hematuria

To develop the risk groupings, the Panel first defined characteristics associated with the lowest and highest risk for urinary tract malignancy. Numerous clinical and demographic factors were incorporated as well into the grouping system, with each placed into a category based on unanimous expert consensus and available published data. For example, the substantially increased risk of malignant diagnosis in patients with a history of GH, compared to MH, has been described in numerous reports.[4,7,22,23,52,54,66-76] Older age and male gender have been consistently associated with increased risk of malignant diagnosis, with several studies supporting relatively greater risks at younger ages for male patients compared to their female counterparts.[7,11,14,65,67,68,77-79] Tobacco exposure has been associated with increased risk of malignant diagnosis, in particular bladder cancer, with associations typically classified at the levels of ever-smoker,[66,67,77] as well as current- or former-smoker,[6] as compared to never smokers. Other forms of tobacco exposure, such as cigars, chewing tobacco and vaporized tobacco products, may also pose a risk for bladder cancer, although the data to date are less robust.

Unique to the AUA Guideline Risk Stratification System is the incorporation of age-specific thresholds for men and women, drawing on observations across the literature of relatively greater risks for male patients at younger ages than their female counterparts.[7,11,14,67,68,77-79] Additionally, this system incorporates stratification based on severity of MH, as large series have found increased risks associated with higher numbers of RBC/HPF[67,78] on microscopic UA. With respect to tobacco exposure, this system incorporates considerations of duration and intensity of tobacco exposure, in

accord with standards from the cancer screening literature. [80,81] Further, the framework provides guidance to recategorize initially low-risk patients with persistent hematuria on follow-up evaluations. Finally, the AUA Guideline Risk Stratification System explicitly incorporates recognized risk factors for urothelial cancer (Table 3) into the considerations for recommending diagnostic evaluation.

The Panel acknowledges that within each of these risk strata, additional features of an individual patient's clinical presentation may influence care. The Panel also appreciates that the intermediate-risk group is somewhat heterogeneous, and the outcomes of patients within this group may still exhibit some variation along the spectrum of risk of urinary tract malignancy. Ultimately, the Panel recognizes the need for prospective validation of these risk groups in large, contemporary patient cohorts in order to further refine performance for identifying underlying urinary tract malignancy.

Urinary Tract Evaluation

Low Risk

Guideline Statement 10

10. In low-risk patients with microhematuria, clinicians should engage patients in shared decision-making to decide between repeating urinalysis within six months or proceeding with cystoscopy and renal ultrasound. (Moderate Recommendation; Evidence Level: Grade C)

Discussion

The Panel acknowledges that the overall rate of urologic malignancy among patients with MH is low, [14] and that the likelihood of diagnosing malignancy in a patient with MH is related to the presence or absence of established cancer risk factors. Limited evidence exists regarding the benefits and risks of evaluating patients at low risk for urologic malignancy with imaging and cystoscopy. The 2019 literature review highlighted the low rate of urologic malignancy in patients presenting with MH, with a reported incidence of 0 to 6.25%. [8-15] For example, Kang et al. determined that, among 911 patients with MH, [11] only 3 (0.3%) had upper tract malignancy— all 3 renal cell carcinoma (RCC). Meanwhile, a Samson et al. study of 1,049 patients with MH found 1 patient (0.1%) with upper tract urothelial carcinoma (UTUC) and 2 patients (0.2%) with RCC, [14] while the Matulewicz et al. series of 15,161 patients with MH noted only 96 patients (0.6%) with an upper tract malignancy. For low-risk patients in particular, the likelihood of upper tract malignancy is exceedingly low.

This low risk of diagnosing a malignancy must be balanced against the potential harms of obtaining imaging, including the implications of false positive detection. In fact, a prior modeling analysis estimated up to a 22% false positive rate in the evaluation of MH, leading to additional evaluation, cost, and patient concern. [17] A separate study of 202 patients undergoing CT urography for MH noted incidental urinary tract findings in 61% and incidental extra-urinary findings in 74%, resulting in additional imaging, referrals to specialists, and hospital costs that totaled nearly $700 per patient. [12] The authors defined an incidental finding as one for which the patient had no prior history and was not related to the reason for the examination. Nevertheless, it should be recognized that some extra-urinary findings may be clinically relevant.

Further, while cystoscopy represents the current standard for diagnosing bladder tumors [52,82-85] with very high sensitivity (98%), [86] it does involve a relatively invasive procedure, with potential attendant patient discomfort and anxiety, as well as a (albeit low) risk of UTI, and, from a healthcare system vantage point, cost. [87,88] The Panel acknowledges that there are several benign conditions that cause MH that may be detected on cystoscopy, such as urethral stricture disease, urethral diverticula, and prostatic enlargement. Nonetheless, these conditions usually present with associated symptoms or signs to prompt a symptom-directed evaluation. Therefore, cystoscopy may not be mandated to identify benign conditions in otherwise asymptomatic patients at low risk for malignancy.

Therefore, the Panel believes that for low-risk MH patients, clinicians should discuss cystoscopy and imaging with renal ultrasound as options for evaluation, but should also review the option to repeat UA, with a plan to escalate to cystoscopy and imaging if the MH is found to persist. The Panel recognizes that many factors will be a part of this shared decision-making process, including patient preferences and risk tolerance. At the same time, the Panel advises that if an initial evaluation is not undertaken, recheck of the UA for persistence of MH should take place. While the Panel recognizes the absence of robust data to prescribe a specific timing of the repeat UA in this setting and acknowledges that patient preferences and risk factors will be incorporated with clinical discretion to guide the process, the Panel would recommend that repeat UA be performed within six months in order to limit the delay in diagnosis of curable malignancy should an underlying cancer be present.

Initially Low-Risk with Hematuria on Repeat Urinalysis

Guideline Statement 11

11. Low-risk patients who initially elected not to undergo cystoscopy or upper tract imaging and who are found to have microhematuria on repeat urine testing should be reclassified as intermediate- or high-risk. In such patients, clinicians should perform cystoscopy and upper tract imaging in accordance with recommendations for these risk strata. (Strong Recommendation; Evidence Level: Grade C)

Discussion

In low-risk patients who do not undergo initial evaluation, the Panel does recommend repeat UA to evaluate for the resolution versus persistence of MH. In one large study, patients who had persistent MH on repeat urine testing had a higher rate of malignancy on subsequent evaluation as compared with those who had negative repeat urine testing. [89]

According to the risk stratification schema previously presented, patients with *persistent* MH are classified as either intermediate or high risk for malignancy, in part dependent upon the degree of MH at the repeat UA (Table 4). 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. The choice of imaging modality involves tradeoffs between diagnostic accuracy versus risk. The Panel believes that the role of cystoscopy and upper tract imaging in the evaluation of the MH patient may be refined

by using the proposed risk stratification structure. Thus, cystoscopy and upper tract imaging are recommended for patients with MH who are at intermediate- or high-risk for malignancy, with the particular imaging modality guided by the patient's risk category.

Intermediate-Risk

Guideline Statement 12

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

Discussion

Studies of MH patients have consistently demonstrated that when a urologic malignancy is detected during evaluation, the most frequent cancer found is bladder cancer. [7,8,10,13-15,21-23,90] As such, cystoscopy should be performed in intermediate-risk MH patients. Regarding the choice of upper tract imaging, 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 as well. [91] However, CT urography is generally more expensive than renal ultrasound and involves ionizing radiation and intravenous contrast. Renal ultrasound is relatively less expensive, does not involve ionizing radiation, and has reasonable discrimination for cortical lesions. On the other hand, image quality is dependent on the operator and the patient's body habitus, and ultrasound has lower sensitivity for urothelial lesions and kidney stones. For UTUC, the sensitivity of CT urography has been reported to be 94%, compared with 14% for renal ultrasound. [4] Additional studies evaluating CT urography reported adequate sensitivity for detection of both cortical tumors (100% sensitivity) and UTUC (80 – 99% sensitivity). [82,92,93] Ultimately, while CT urography has been found to offer the optimal detection of upper tract malignancy, [17] the use of this modality must be balanced with the overall low rate of malignancy in MH patients, [5] as well as the potential harms associated with CT, including ionizing radiation, intravenous contrast reactions, and false-positive results. [17,94-96] Thus, the Panel recommends a risk-based approach to MH evaluation, using renal ultrasound for intermediate-risk patients and CT urography for high-risk patients. At the same time, cystoscopy represents a critical component of the MH evaluation given the limited sensitivity of CT and ultrasound for identifying bladder cancer. [4,52,76]

Notably, given the overall population-level prevalence of MH, healthcare resource allocation is impacted by the choice of imaging to evaluate these patients. Indeed, Halpern et al. evaluated the cost of CT urography plus cystoscopy versus renal ultrasound plus cystoscopy in a theoretical population of 10,000 patients with MH and found the overall cost was over three times greater for the CT group despite only detecting one additional UTUC. [18]

Meanwhile, a recent modeling study determined that for a cohort of 100,000 patients with hematuria, [17] there would be a total of 93 patients with UTUC (0.09%) versus 443 (0.44%) patients with RCC. This study concluded that while the less intense evaluation (e.g., renal ultrasound) risks missing a very small number of upper tract malignancies

compared to a more intense evaluation (e.g., CT), routine use of renal ultrasound instead of CT urography for all patients would decrease costs and patient radiation exposure. [17] The Panel believes the risk of 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 in this patient group.

High-Risk

Guideline Statement 13

13. Clinicians should perform cystoscopy and axial upper tract imaging in patients with microhematuria categorized as high-risk for malignancy. (Strong Recommendation; Evidence Level: Grade C)

Options for Upper Tract Imaging in High-Risk Patients:

a. If there are no contraindications to its use, clinicians should perform multiphasic CT urography (including imaging of the urothelium). (Moderate Recommendation; Evidence Level: Grade C)

b. If there are contraindications to multiphasic CT urography, clinicians may utilize MR urography. (Moderate Recommendation; Evidence Level: Grade C)

c. If there are contraindications to multiphasic CT urography and MR urography, clinicians may utilize retrograde pyelography in conjunction with non-contrast axial imaging or renal ultrasound. (Expert Opinion)

Discussion

As previously stated, cystoscopy represents a critical component of the MH evaluation because imaging with CT urogram or ultrasound has limited sensitivity for identifying bladder cancer. [4,76] As such, the Panel views cystoscopy as an important part of the work-up of patients with MH identified as high-risk for malignancy.

The Panel concluded that patients who meet the high-risk criteria are at a sufficient risk for harboring a diagnosis of urothelial cancer to also warrant multiphasic cross-sectional imaging to evaluate both the renal parenchyma and the urothelium, using CT urography if there are no contraindications to its use. Of note, while multiple protocols fall under the moniker of CT urography, the overall intent of these studies is to provide unenhanced and enhanced views of the kidneys to identify renal cortical tumors and determine whether they enhance; and to provide delayed views of the renal collecting systems and ureters in order to identify upper tract urothelial tumors. A host of additional urinary tract and extra-urinary findings may also be identified, including urinary lithiasis and anatomic abnormalities. Given the range of options available for evaluation of the renal parenchyma and upper tract urothelium with CT and the absence of strong evidence to support one technique over another, the Panel recommends using a protocol that optimizes imaging performance characteristics while minimizing radiation exposure. While there is not to date a single practiced standardized dose reduction strategy, options include split bolus protocols and radiation dosage adjustment for body mass index (BMI). [97]

Contraindications to contrast-enhanced CT include chronic kidney disease and allergy to iodine-based contrast. In such patients, the Panel recommends magnetic resonance (MR) urography as an alternative imaging modality. Pregnant patients constitute a unique population for which there are little data for guidance. Since few pregnant patients will fall into the high risk group, the Panel recommends initially obtaining renal ultrasonography for MH during pregnancy, with consideration of multiphasic CT or MR urography after delivery.

MR urography has adequate sensitivity for renal cortical tumors and upper tract urothelial tumors, but lower sensitivity for nephrolithiasis. [98] Harms and limitations of MR urography include risk of false positive results, inconvenience of the lengthy exam, cost, limited accessibility, and risk of nephrogenic systemic fibrosis (NSF). In addition, contraindications to MR urography include metal implants and claustrophobia. Of note, NSF was initially described in patients with poor renal function receiving gadolinium for MRI studies; however, contemporary rates of NSF have decreased, likely due to awareness of the risk and the development of newer gadolinium-based contrast agents. [99,100] Indeed, the American College of Radiology issued recommendations in 2018 that relax the concern for NSF, particularly with the use of newer gadolinium agents (e.g., gadobutrol, gadoxetate), even in patients with low renal function. [101] Ultimately, if MR urogram is being considered for a patient with poor renal function and MH, the Panel recommends discussion with institutional radiologists regarding the agent being used on site and the relative risk-yield ratio of the study. Moreover, it should be acknowledged that MRI has a lower detection rate than CT for the detection of stone disease. Therefore, if nephrolithiasis is suspected based on the patient's history, then non-contrast CT should be undertaken.

For patients with contraindications to CT and MR urography, imaging of the renal cortex may be achieved with either non-contrast CT or renal ultrasound to assess the renal cortex and retrograde pyelography (RPG) to assess the urothelium.

Guideline Statement 14

14. Clinicians should perform white light cystoscopy in patients undergoing evaluation of the bladder for microhematuria. (Moderate Recommendation; Evidence Level: Grade C)

Discussion

White light cystoscopy (WLC) remains the standard for evaluation of MH. [102] The Panel recognizes that the reliability of WLC for the detection of flat lesions (i.e., carcinoma in situ [CIS]) is reduced relative to papillary tumors, with a false-negative rate as high as 20%. [103-105] Further, the Panel acknowledges the development of enhanced cystoscopic techniques such as blue light cystoscopy (BLC) to improve bladder cancer detection and resection among patients previously diagnosed with bladder cancer. [106,107] Indeed, BLC has been associated with several benefits, including improved detection of CIS and papillary tumors as well as reduction in disease recurrence compared with WLC in patients with bladder cancer. [104,108]

Nevertheless, BLC studies to date have been reported among patients with bladder cancer rather than MH cohorts being screened for bladder cancer. As such, the generalizability of this approach to MH patients remains uncertain. In addition, the

available studies have noted a somewhat reduced specificity for BLC compared with WLC, which in turn could lead to an increased rate of unnecessary biopsy. Moreover, BLC involves additional cost and time expenditure, and has not been widely validated for flexible cystoscopy.

Thus, given the lack of evidence supporting a role for enhanced cystoscopy to evaluate MH patients in the absence of an established bladder cancer diagnosis, the Panel concludes that WLC should be utilized in the evaluation of MH.

Guideline Statement 15

15. In patients with persistent or recurrent microhematuria previously evaluated with renal ultrasound, clinicians may perform additional imaging of the urinary tract. (Conditional Recommendation; Evidence Level: Grade C)

Discussion

While renal ultrasound provides an evaluation of the renal cortex, the sensitivity of this modality for detecting ureteral pathology, in particular UTUC, is diminished. [4,94,109] The patient with persistent or recurrent MH who has undergone prior renal ultrasound represents a clinical scenario in which the diagnosis of UTUC is possible, although admittedly still uncommon. Nevertheless, in these cases, clinicians may choose to obtain further imaging to include delineation of the urothelium such as CT urography, MR urography, or RPG.

Guideline Statement 16

16. In patients with microhematuria who have a family history of renal cell carcinoma or a known genetic renal tumor syndrome, clinicians should perform upper tract imaging regardless of risk category. (Expert Opinion)

Discussion

RCC is associated with several genetic syndromes (Table 5 [110-113] and with a family history of RCC.,sup>50 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.

Table 5: Inherited risk factors for renal cortical tumors
Known genetic renal tumor syndrome

Table 5: Inherited risk factors for renal cortical tumors

1. von Hippel-Lindau
2. Birt-Hogg-Dube
3. Hereditary Papillary RCC
4. Hereditary Leiomyomatosis Renal Cell Cancer
5. tuberous sclerosis

Urinary Markers

Guideline Statement 17

17. Clinicians should not use urine cytology or urine-based tumor markers in the initial evaluation of patients with microhematuria. (Strong Recommendation; Evidence Level: Grade C)

Guideline Statement 18

18. Clinicians may obtain urine cytology for patients with persistent microhematuria after a negative workup who have irritative voiding symptoms or risk factors for carcinoma in situ. (Expert Opinion)

Discussion

The Panel does not recommend using urine cytology or urine-based tumor markers in the initial evaluation of MH since insufficient evidence exists that routine use would improve detection of bladder cancer. Indeed, to demonstrate that a marker would provide incrementally additive information to cystoscopy, future studies will need to show that a meaningful number of cancers would be found in patients where cystoscopy was normal and a biomarker was positive. Currently, such data do not exist, and, in fact, limited data exist to support an additive clinical benefit of cytology or urine markers in patients undergoing cystoscopy to detect bladder cancer. For example, a prospective study of 2,778 patients evaluated the added benefit of obtaining cytology during the initial evaluation of MH. [114] Of the 2,778 patients, only two with a negative evaluation (cystoscopy, ultrasound and Intravenous pyelogram) and a positive cytology were eventually diagnosed as having urothelial carcinoma. In addition, there are costs associated with the 10.5% false-positive rate from cytology, 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 CIS and 2 had upper tract disease. Meanwhile, the DETECT I study recruited 3,556 patients presenting with hematuria (30.3% MH, 69.7% GH), of whom urine cytology was performed in 567 (15.9%). [115] A positive/atypical urinary cytology was reported to have a sensitivity of 57.7%, specificity 94.9%, PPV 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. Collectively, therefore, data to date indicate that cytology rarely identifies cancer in the setting of normal cystoscopy and imaging.

One area for which cytology may have a role is in improving detection of CIS. In particular, it has been recognized that WLC may fail to identify some bladder cancers, especially CIS. [116] For example, in a prospective cohort study enrolling MH and GH patients, the diagnostic sensitivity of cytology was 57.7% (95%CI 38.7 to 75.3) for high-risk bladder cancers. [115] As such, there may be a role for cytology in patients with persistent MH in patients who have irritative voiding symptoms or other risk factors for CIS. Similarly, while urine markers 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. A systematic review with meta-analysis assessed the diagnostic test characteristics of FDA-approved urinary biomarker assays for detection of bladder cancer. [117] The systematic review included 14 studies, including two for AssureMDx, two for BTA, one for CxBladder, four for qualitative NMP22, five for quantitative NMP22, two for uCyt+, one for UroVysion, and nine for cytology. A concern regarding these studies is the lack of a true comparative analysis of markers, as in several cases the series represent case-control studies. The strength of the body of evidence underpinning the use of urine-based tumor markers was graded Level C. The aggregate risk of bias across all included studies was critical, and in addition the evidence was downgraded for inconsistency of results. A further limitation of the studies is a lack of evaluation concerning whether these markers add information independent of the cystoscopy itself.

An important component of the current guideline is to offer a risk-stratified approach to the type and intensity of evaluation for patients with MH. To date, few studies have evaluated the role of markers to improve risk stratification, and the strength of evidence of these few studies remains insufficient to recommend them currently. The potential future role for markers in risk stratification is addressed in Future Directions.

Follow Up

Guideline Statement 19

19. In patients with a negative hematuria evaluation, clinicians may obtain a repeat urinalysis within 12 months. (Conditional Recommendation; Evidence Level: Grade C)

Guideline Statement 20

20. For patients with a prior negative hematuria evaluation and subsequent negative urinalysis, clinicians may discontinue further evaluation for microhematuria. (Conditional Recommendation; Evidence Level: Grade C)

Guideline Statement 21

21. For patients with a prior negative hematuria evaluation who have persistent or recurrent microhematuria at the time of repeat urinalysis, clinicians should engage in shared decision-making regarding need for additional evaluation. (Expert Opinion)

Guideline Statement 22

22. For patients with a prior negative hematuria evaluation who develop gross hematuria, significant increase in degree of microhematuria, or new urologic symptoms, clinicians should initiate further evaluation. (Moderate Recommendation; Evidence Level: Grade C)

Discussion

The decision to follow patients after completion of a negative hematuria evaluation represents a balance of various considerations. Relevant factors include the potential to subsequently detect a previously undiagnosed urologic malignancy or clinically significant urologic condition, as well as the potential to detect a malignancy or clinically significant urologic condition that the patient develops following initial hematuria evaluation. In addition, clinicians may be concerned about dismissing a patient from care, including worries over medicolegal implications. These putative benefits must be contextualized, however, with the repeated anxiety and inconvenience to the patient of continued monitoring, as well as the increased costs to the healthcare system of additional investigation.

Importantly, moreover, the very limited diagnostic yield of repeated evaluations noted to date from studies of patients followed after a negative hematuria evaluation must also be recognized. Indeed, among 148 patients who underwent repeat CT urogram within three years after prior CT urogram, none of the 103 patients whose initial scan was without suspicious findings demonstrated malignancy on the second imaging study, while among the 45 patients with suspicious initial CT urogram findings, 4 malignancies were diagnosed, 3 of which were in fact incidental to the initial suspicious finding. [118] Likewise, a series of 87 patients followed after a negative hematuria evaluation reported that, despite all 87 patients having persistent MH, the only malignancy diagnosed at three years of follow-up was a single prostate cancer. [119] Similarly, in a study with a mean 14-year follow-up of 258 men age ≥50 years with MH who had a negative complete initial evaluation, only two bladder cancers were subsequently diagnosed at 6.7 years and 11.4 years of follow-up, respectively. [120] Although the modest sample size of these reports precludes definitive conclusions, such data should be considered when discussing the plan for follow-up with patients.

At the same time, the Panel recognizes that selected patients may benefit from and/or request follow-up after a negative hematuria evaluation, or after a negative follow-up UA in a low-risk patient who has not been evaluated. A repeat UA represents an initial, non-invasive modality for continued monitoring. To avoid prolonged delays if an undiagnosed malignancy were present, the Panel offers that this subsequent UA be performed within 12 months of the initial evaluation. Patients with a negative follow-up UA may be discharged from further hematuria evaluation given the very low risk of malignancy, while patients with persistent MH merit shared decision-making regarding next steps in care. Importantly, changes in a patient's clinical status should prompt clinical review. Specifically, given the associations noted between the presence of GH, [4,22,23,52-54,66,68-76,121-123] higher degrees of MH, [13,76,78] and urologic symptoms [22,69] with the diagnosis of malignancy or clinically significant benign conditions, presentation with any of these should merit further evaluation. 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.

Patients with causes of MH that persist and may not require intervention, such as those with enlarged prostates and friable surface vessels, those with Randall's plaques and non-obstructing stones, women with pelvic organ prolapse or vaginal atrophy, present a special challenge since malignant causes of MH may be masked by the present of these other entities. Ultimately, clinicians' judgement and patient preferences are critical in the shared decision-making process regarding the timing and components of further evaluation among patients with persistent or recurrent hematuria.

Future Directions

The goal of this guideline is to improve the evaluation and management of patients with hematuria. Due to the combination of a relatively high prevalence of MH in the adult population with a low likelihood of identifying clinically-significant disease, this guideline aims to provide a risk-based framework for testing. Moreover, it is recognized that many patients with hematuria are not currently undergoing evaluation, and thus another goal of risk-based recommendations is to improve utilization of the guideline by patients and clinicians. Nevertheless, the Panel recognizes the paucity of high-level supporting evidence for the guideline statements, and acknowledges several notable areas where gaps in knowledge exist, which represent opportunities for future investigation to meaningfully enhance care.

For example, new automated instruments, based either on flow cytometry or digitized microscopy, are increasingly utilized to perform UA. These machines may not correlate directly with traditional urine microscopy, and thus it will be important to determine if the threshold of 3RBC/HPF used in the guideline will be an equivalent predictor of risk when these new technologies are used in evaluation. [124]

One area of particular importance for additional study will be to validate the risk groups that have been outlined herein. Specifically, it remains to be determined whether these current divisions between risk groups accurately reflect differences in cancer risk. Ideally, large prospective cohort studies will form the basis for such validation. Moreover, the current risk stratification focuses primarily on risk factors for urothelial cancer. That is, smoking, obesity, hypertension, and chronic kidney disease represent established risk factors for RCC, of which only smoking is represented in current risk stratification. [25] Whether a different risk stratification is necessary to improve recommendations regarding imaging will also require further study. The potential benefits of reducing exposure to radiation and contrast agents (with attendant risk of renal issues and allergies) and decreasing healthcare cost are substantial; [17,18,94] however, there exists the risk with this approach of missing small renal masses, upper tract urothelial cancers, and small stones. [4,17,52,109,126] The balance of these pros and cons will need to be determined. At the same time, the potential health system benefits of a risk-based approach, as well as implementation/adherence to the guideline recommendations, will need to be documented.

Another topic that merits continued investigation is the potential role of urinary biomarkers in the evaluation of patients with MH. Urothelial cancers are in contact with the urine, and this fact has been utilized to evaluate the differential expression of proteins, RNA, DNA, and changes in methylation and cells among patients with malignant and benign conditions. There are multiple markers currently available and in development to help with detection of bladder cancer in hematuria patients. While there is insufficient evidence to recommend use of these markers routinely in the evaluation of patients with MH, the potential exists for these

markers to improve risk stratification over the clinical variables put forth herein, and thereby improve an individualized approach to MH evaluation. For example, biomarkers may in the future be used to calculate a pre-test probability of finding urothelial carcinoma, which may in turn guide the intensity of subsequent evaluation. If, for example, a negative test result yields a pre-test probability of <1% of malignancy in a patient, perhaps the patient and doctor would opt to forego cystoscopy, whereas if a positive result raises the pre-test probability to 5% or higher, they would decide to pursue cystoscopy. In order to adopt a risk-stratified approach incorporating markers, future studies will be necessary to determine if urine markers improve risk stratification. A prospective randomized trial is currently open that randomizes patients based on clinical risk and marker status (NCT03988309). Patients in the marker arm will have a clinical risk stratification, such that patients with low clinical risk and a negative marker will not have cystoscopy but follow-up only, while those with a positive marker or higher risk based on clinical factors will undergo a standard evaluation with cystoscopy. This marker-based approach will be compared to a standard evaluation in the control arm. Such randomized trials will provide the strength of evidence needed to establish a role for markers in patients with hematuria.

Another area worthy of further evaluation is whether enhanced cystoscopy has a role in the detection of bladder cancer among patients with hematuria. The current Non-Muscle Invasive Bladder Cancer (NMIBC) AUA Guideline recognizes that enhanced cystoscopy can improve detection of bladder cancer. [127] The NMIBC Guideline gave a moderate recommendation that a clinician should offer BLC at the time of TURBT, if available, to increase detection and decrease recurrence of bladder cancer, and provided a conditional recommendation regarding use of narrow band imaging (NBI). However, there is insufficient evidence with regard to the role of enhanced cystoscopy in hematuria patients without an established bladder cancer diagnosis. [128] Thus, the question remains whether the added cost, capital equipment, and logistical issues, as well as risk for false positive results, [129,130] justifies use in the detection setting.

Opportunities to reduce radiation exposure with imaging represents another ongoing focus of investigation. [131,132] Indeed, the need remains to determine whether using lower doses of radiation provides similar sensitivity to detect benign and malignant urologic findings, and which, if any, patient populations or risk groups would be particularly suited for such modified protocols.

The natural history – and, as an extension, the recommended follow-up – of patients with hematuria following a completed, negative evaluation also represents a relevant topic for future study. Many patients with MH will have persistent findings of microscopic blood – likely due to benign causes that may or may not be recognized – and the optimal approach to these patients has not been established. Continued evaluations risk patient anxiety as well as potentially unnecessary resource allocation. These concerns are likewise relevant for low-risk patients who initially choose surveillance rather than evaluation.

Overall, the current guideline represents an effort to improve the detection of clinically significant disease while reducing the indiscriminant allocation of healthcare resource and subjecting patients to tests with risk and attendant discomfort/anxiety. Hematuria 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 intensity and frequency of evaluation will need to be studied to determine if the utilization of recommendations has improved.

Abbreviations

ACOG American College of Obstetricians and Gynecologists

AUA	American Urological Association
BCAN	Bladder Cancer Advocacy Network
BLC	Blue light cycstoscopy
BMI	Body mass index
BOD	Board of Directors
BPH	Benign prostatic hyperplasia
CIS	Carcinoma in situ
CT	Computed tomography
GH	Gross hematuria
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HCRS	Hematuria Cancer Risk Score
HPF	High-power field
HRI	Hematuria Risk Index
MH	Microhematuria
MR	Magnetic resonance
NBI	Narrow Band Imaging
NMIBC	Non-muscle invasive bladder cancer
NPV	Negative predicitve value
NSF	Nephrogenic predictive value
PGC	Practice Guidelines Committee
PICO	Populations, interventions, comparators, and outcomes
PPV	Positive predictive value
RBC	Red blood cell
RCC	Renal cell carcinoma
RCT	Randomized controlled trial
ROC	Receiver Operating Characteristics
RPG	Retrograde pyelography
SQC	Science & Quality Council
SUFU	Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction
UA	Urinalysis
UTI	Urinary Tract Infection
UTUC	Upper tract urothelial carcinoma
WLC	White light cystoscopy

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