Microhematuria: AUA/SUFU Guideline

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MeSH

hematuria; cystoscopy; CT Urogram; bladder cancer; urothelial carcinoma; urine markers

Abbreviations

1. CIS   Carcinoma in situ
2. GRADE   Grading of Recommendations, Assessment, Development, and Evaluation
3. MH   Microhematuria
4. RBC/HPF   Red blood cells per high-power field
5. RCC   Renal cell carcinoma
6. UA   Urinalysis
7. UTUC   Upper tract urothelial carcinoma

Abstract

Purpose

Patients presenting with microhematuria represent a heterogeneous population with a broad spectrum of risk for genitourinary malignancy. Recognizing that patient-specific characteristics modify the risk of underlying malignant etiologies, this guideline sought to provide a personalized diagnostic testing strategy.

Materials and Methods

The systematic review incorporated evidence published from January 2010 through February 2019, with an updated literature search to include studies published up to December 2019. Evidence-based statements were developed by the expert Panel, with statement type linked to evidence strength, level of certainty, and the Panel's judgment regarding the balance between benefits and risks/burdens.

Results

Microhematuria should be defined as ≥ 3 red blood cells per high power field on microscopic evaluation of a single specimen. 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. The Panel created a risk classification system for patients with microhematuria, stratified as low-, intermediate-, or high-risk for genitourinary malignancy. Risk groups were based on factors including age, sex, smoking and other urothelial cancer risk factors, degree and persistence of microhematuria, as well as prior gross hematuria. Diagnostic evaluation with cystoscopy and upper tract imaging was recommended according to patient risk and involving shared decision-making. Statements also inform follow-up after a negative microhematuria evaluation.

Conclusions

Patients with microhematuria should be classified based on their risk of genitourinary malignancy and evaluated with a risk-based strategy. Future high-quality studies are required to improve the care of these patients.

Introduction

Hematuria is 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]

The differential diagnosis of MH encompasses a wide range of urologic, nephrologic, as well as gynecologic conditions. Importantly, while genitourinary malignancy has been diagnosed in approximately 3% of patients evaluated for MH,[2,3] the risk of detecting an underlying cancer has been found to be highly dependent on factors such as sex, age, smoking history, and degree of hematuria.[4]

As the aggregate likelihood of identifying a malignancy among patients with MH is relatively low, the benefits and potential harms of diagnostic evaluation must be considered both at the patient and health system level.

At the same time, practice-pattern assessments have demonstrated significant deficiencies 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.[5] Furthermore, performance of both cystoscopy and imaging occurs in less than 20% of patients in most series, and varies to some degree by sex and race.[6-8] The underuse of cystoscopy, and the tendency to rely solely on imaging for evaluation, is particularly concerning since the vast majority of cancers diagnosed among persons with hematuria are bladder cancers, optimally detected with cystoscopy.[4,6-14]

As such, there is a need for updated, evidence-based 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 clearly identifying clinical scenarios in which work-up is warranted in order to address the delays in diagnosis of important urologic conditions. In addition, 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."[15] The purpose of this guideline and the associated algorithm (Figure 1) is, therefore, to provide a clinical framework for the diagnosis, evaluation, and follow-up of MH.

Methodology

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 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. 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.

Determination of Evidence Strength

Certainty of evidence underpinning the recommendation statements were defined using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system. The AUA employs a three-tiered strength of evidence system to inform evidence-based guideline statements.[16] 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)

AUA Nomenclature: Linking Statement Type to Evidence Strength

The AUA nomenclature system explicitly links statement type to the 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).

A full description of the AUA methodology system can be found in the unabridged version of this guideline available at www.auanet.org/guidelines.

Guideline Statements

Diagnosis and Definition of Microhematuria (MH)

1. **Clinicians should define MH as $\geq$3 red blood cells per high-power field (RBC/HPF) on microscopic evaluation of a single, properly collected urine specimen. (Strong Recommendation; Evidence Level: Grade C)**

2. **Clinicians should not define MH 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)**

The literature review from the 2012 guideline and more recent data support the definition of MH as $\geq$ 3 RBC/HPF on microscopic evaluation of a single urine specimen.[2,17] Dipstick testing remains insufficient as it measures peroxidase activity, which can be confounded by factors including (but not limited to) the use of povidone iodine, myoglobinuria, and dehydration. In order to inform clinicians of the degree of hematuria a patient has with sufficient detail to determine whether further evaluation is warranted, the Panel emphasizes the importance of utilizing laboratories reporting RBC/HPF quantitatively.

Initial Evaluation

3. **In patients with MH, 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 MH. (Clinical Principle)**

Careful consideration should be given to risk factors for malignancy (Tables 3 and 4). 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 MH.

4. **Clinicians should perform the same evaluation of patients with MH 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)**

Patients on anticoagulants should be assessed in the same fashion as patients who are not anticoagulated because these patients have a malignancy risk similar to other populations.[18-20]

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 MH, clinicians should repeat urinalysis (UA) following resolution of the gynecologic or non-malignant genitourinary cause. If MH 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 UA with microscopic evaluation following treatment to ensure resolution of the hematuria. (Strong Recommendation; Evidence Level: Grade C)**

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.

In light of noted practice patterns, the Panel believes it is important to emphasize the need for a follow-up UA following resolution of a presumed gynecologic or non-malignant urologic cause of MH, particularly urinary tract infection, to confirm resolution of the MH. If the MH persists, a risk-based urologic evaluation should be performed.

The Panel acknowledges that there are some non-malignant urologic and gynecologic conditions, such as non-obstructing nephrolithiasis 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 guide these decisions.

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

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 for risk-based urologic evaluation to identify coexistent urologic pathology.

Risk Stratification

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

Patients presenting with hematuria represent a heterogeneous population with a broad spectrum of risk for underlying malignancy based on clinical and demographic features. The Panel, therefore, created categories, summarized as 'low-,' 'intermediate-,' and 'high-' risk for a diagnosis of genitourinary malignancy (Table 4), in order to facilitate patient-centered testing strategies.

Several available risk stratification systems were considered, which, broadly stated, estimate risk of urothelial carcinoma as <1% for those deemed low-risk, 1-2% for intermediate-risk, and 10% or greater for high-risk.[4,21] The Panel also considered the contribution to patient risk of each individual risk factor for urothelial carcinoma based on an extensive literature review. The risk stratification system designed for this guideline was based on this systematic review and received unanimous approval from members of the Panel.

Recognizing that there remains variability in risk *within* each risk group and that this classification system will require validation, several strengths merit highlighting. First, the stratification incorporates age-specific thresholds for men and women, drawing on observations of greater risk for malignancy for male patients at younger ages than their female counterparts.[4,9,22-27] Additionally, this system incorporates stratification based on degree of MH, as large series have found increased risks associated with higher numbers of RBC/HPF on microscopic UA.[23,26] 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.[28,29] 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.

Urinary Tract Evaluation

Low-Risk

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

The Panel acknowledges that the likelihood of diagnosing malignancy in a low-risk MH patient is very low; therefore, the diagnostic yield in such patients must be balanced against the potential harms of obtaining imaging, including the implications of false positive detection.[30]

Further, while cystoscopy represents the current standard for diagnosing bladder tumors[31-34] it does involve a relatively invasive procedure, with potential patient discomfort and anxiety, as well as a low risk of UTI, and, from a healthcare system vantage point, cost.[35,36]

Understanding then that some low-risk patients may choose to repeat a UA rather than undergo evaluation at the time of initial MH diagnosis, the Panel advises a repeat UA within six months to limit the likelihood of delayed diagnosis of a treatable urologic condition.

Initially Low-Risk with Hematuria on Repeat Urinalysis (UA)

11. **Low-risk patients who initially elected not to undergo cystoscopy or upper tract imaging and who are found to have MH 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)**

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.[37] According to the risk stratification schema above, patients with *persistent* MH are, therefore, re-classified as either intermediate- or high-risk for malignancy, in part dependent upon the degree of MH present at the repeat UA (Table 4). Such re-classification ensures that patients with recurrent or persistent hematuria undergo a risk-stratified evaluation.

Intermediate-Risk

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

Studies of MH patients have consistently demonstrated that when a urologic malignancy is detected during evaluation, the most frequent cancer found is bladder cancer.[4,6-14,] Whereas imaging has poor sensitivity for identifying bladder cancer,[4] cystoscopy is 98% sensitive.[38] As such, cystoscopy should be performed in intermediate-risk MH patients. Regarding the choice of upper tract imaging, renal ultrasound has adequate sensitivity and specificity for renal cortical tumors compared to axial imaging, at lower cost and with less risk (e.g., ionizing radiation, intravenous contrast reactions, and false-positive results).[30,39-41] While the reported sensitivity of renal ultrasound for upper tract urothelial carcinoma (UTUC) is poor (14%), the Panel's recommendation here is based on the low incidence of this diagnosis,[24] and, therefore, limited benefit of axial imaging over ultrasound.

High-Risk

13. **Clinicians should perform cystoscopy and axial upper tract imaging in patients with MH 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 <u>no</u> contraindications to its use, clinicians should perform multiphasic CT urography (including imaging of the urothelium). (Moderate Recommendation; Evidence Level: Grade C)**
   b. **If there <u>are</u> 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 <u>and</u> MR urography, clinicians may utilize retrograde pyelography in conjunction with non-contrast axial imaging or renal ultrasound. (Expert Opinion)**

Cystoscopy is a critical component of the work-up of patients with MH identified as high-risk for malignancy because of the risk of bladder cancer in this population.

The Panel concluded that patients who meet the high-risk criteria are at a sufficient risk for harboring an upper tract malignancy 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.

In patients with contraindications to contrast-enhanced CT, such as chronic kidney disease or allergy to iodine-based contrast, the Panel recommends MR urography.

For patients with contraindications to both CT and MR urography, either non-contrast CT or renal ultrasound may be used to assess the renal cortex with the addition of retrograde pyelography to assess the upper urinary tracts.

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

White light cystoscopy remains the standard for evaluation of MH.[42] The Panel acknowledges the development of enhanced cystoscopic techniques such as blue light cystoscopy to improve bladder cancer detection and resection among patients previously diagnosed with bladder cancer.[43,44] Nevertheless, blue light cystoscopy studies to date have been reported among patients with an established diagnosis of bladder cancer rather than MH cohorts being screened for bladder cancer. As such, the generalizability of this approach to MH patients remains uncertain.

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

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. In these cases, clinicians may choose to obtain further imaging to include delineation of the urothelium such as CT urography, MR urography, or retrograde pyelography.

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

RCC is associated with several genetic syndromes (Table 5)[45-48] and with a family history of RCC;[49] therefore, such patients who have MH should undergo upper tract imaging. Insufficient evidence exists regarding the preferred modality in this scenario.

Urinary Markers

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

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

The Panel does not recommend using urine cytology or urine-based tumor markers in the initial evaluation of MH because, to date, markers have not demonstrated incrementally additive information to cystoscopy in the MH population, nor have they been found to be of sufficient predictive value to obviate cystoscopy.

One area for which cytology may have a role is in improving detection of carcinoma in situ (CIS), which occasionally may evade detection by white light cystoscopy.[50] 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.

Follow-Up

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

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

21. **For patients with a prior negative hematuria evaluation who have persistent or recurrent MH at the time of repeat UA, 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 MH, or new urologic symptoms, clinicians should initiate further evaluation. (Moderate Recommendation; Evidence Level: Grade C)**

The intensity of follow-up after completion of a negative hematuria evaluation must balance the small risk of a false-negative initial evaluation with the anxiety, cost, inconvenience, and risks of ongoing monitoring and repeat investigation.

The very limited diagnostic yield of repeated evaluations noted to date from studies of patients followed after a negative hematuria evaluation must be recognized. However, the Panel recognizes that select 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. 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, particularly the development of gross hematuria, should prompt clinical review.

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 prevalence of clinically-significant disease, this guideline aims to provide a risk-based framework for testing. Moreover, it is recognized that, in the current state, many patients with hematuria do not undergo evaluation. Accordingly, an important goal of risk-based recommendations is to provide guidance for patients and clinicians regarding appropriate evaluation. 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. These represent opportunities for future investigation to meaningfully enhance care. Such areas include the use of new automated instruments for UA, validation of risk groups, utility of urinary biomarkers and enhanced cystoscopy for MH, refinement of imaging techniques to reduce radiation exposure, and further investigation of the natural history of patients with MH following negative evaluation.

References

1. Mariani AJ, Mariani MC, Macchioni C et al: The significance of adult hematuria: 1,000 hematuria evaluations including a risk-benefit and cost-effectiveness analysis. J Urol 1989; **141**:350.

2. Davis R, Jones JS, Barocas DA, Castle EP, Lang EK, Leveillee RJ, et al. Diagnosis, evaluation and follow-up of asymptomatic microhematuria (AMH) in adults: AUA guideline. J Urol 2012; **188**:2473.

3. Tan WS, Sarpong R, Khetrapal P et al: Can renal and bladder ultrasound replace computerized tomography urogram in patients investigated for microscopic hematuria? J Urol 2018; **200**:973.

4. Loo RK, Lieberman SF, Slezak JM et al: Stratifying risk of urinary tract malignant tumors in patients with asymptomatic microscopic hematuria. Mayo Clin Proc 2013; **88**:129.

5. Johnson EK, Daignault S, Zhang Y et al: Patterns of hematuria referral to urologists: does a gender disparity exist? Urology 2008; **72**: 498.

6. Aguilar-Davidov B, Ramirez-Mucino A, Culebro-Garcia C et al: Performance of computed tomographic urography for the detection of bladder tumors in patients with microscopic hematuria. Actas Urol Esp 2013; **37**:408.

7. Elias K, Svatek RS, Gupta S et al: High-risk patients with hematuria are not evaluated according to guideline recommendations. Cancer 2010; **116**:2954.

8. Matulewicz RS, Demzik AL, DeLancey JO et al: Disparities in the diagnostic evaluation of microhematuria and implications for the detection of urologic malignancy. Urol Oncol 2019;**17**:17.

9. Samson P, Waingankar N, Shah P et al: Predictors of genitourinary malignancy in patients with asymptomatic microscopic hematuria. Urol Oncol 2018; **36**:10.e1.

10. Sundelin MO, Jensen JB: Asymptomatic microscopic hematuria as a predictor of neoplasia in the urinary tract. Scand J Urol 2017; **51**:373.

11. Todenhofer T, Hennenlotter J, Tews V et al: Impact of different grades of microscopic hematuria on the performance of urine-based markers for the detection of urothelial carcinoma. Urol Oncol 2013; **31**:1148

12. Koo KC, Lee KS, Choi AR et al: Diagnostic impact of dysmorphic red blood cells on evaluating microscopic hematuria: the urologist's perspective. Int Urol Nephrol 2016; **48**:1021.

13. Bromage SJ, Liew M, Moore K et al: The evaluation of CT urography in the haematuria clinic. J Clin Urol 2013; **6**:153.

14. Eisenhardt A, Heinemann D, Rubben H et al: Haematuria work-up in general care-a German observational study. Int J Clin Pract 2017; **71**: Epub.

15. Wennberg JE: Unwarranted variations in healthcare delivery: implications for academic medical centres. BMJ 2002; **325**: 961.

16. Faraday M, Hubbard H, Kosiak B et al: Staying at the cutting edge: a review and analysis of evidence reporting and grading; the recommendations of the American Urological Association. BJU Int 2009; **104**: 294.

17. Matulewicz RS, DeLancey JO, Pavey E et al: Dipstick urinalysis as a test for microhematuria and occult bladder cancer. Bladder Cancer 2017; **3**:45.

18. Khadra MH, Pickard RS, Charlton M et al: A prospective analysis of 1,930 patients with hematuria to evaluate current diagnostic practice. J Urol 2000; **163**:524.

19. Jeong CW, Lee S, Byun SS et al: No increase in risk of microscopic hematuria with aspirin use by asymptomatic healthy people. JAMA Intern Med 2013; **173**:1145.

20. Culclasure TF, Bray VJ, Hasbargen JA et al: The significance of hematuria in the anticoagulated patient. Arch Int Med 1994; **154**:649.

21. Tan WS, Ahmad A, Feber A et al: Development and validation of a haematuria cancer risk score to identify patients at risk of harbouring cancer.J Intern Med 2019; **285**: 436.

22. Kang M, Lee S, Jeong SJ et al: Characteristics and significant predictors of detecting underlying diseases in adults with asymptomatic microscopic hematuria: a large case series of a Korean population. Int J Urol 2015; **22**:389.

23. Lippmann QK, Slezak JM, Menefee SA et al: Evaluation of microscopic hematuria and risk of urologic cancer in female patients. Am J Obstet Gynecol 2017; **216**:146.e1.

24. Commander CW, Johnson DC, Raynor MC et al: Detection of upper tract urothelial malignancies by computed tomography urography in patients referred for hematuria at a large tertiary referral center. Urology 2017; **102**:31.

25. Hee Tan G, Shah SA, Ann HS et al: Stratifying patients with haematuria into high or low risk groups for bladder cancer: a novel clinical scoring system. Asian Pac J Cancer Prev 2013; **14**:6327.

26. Jung H, Gleason JM, Loo RK et al: Association of hematuria on microscopic urinalysis and risk of urinary tract cancer. J Urol 2011; **185**:1698.

27. Elmussareh M, Young M, Ordell Sundelin M et al: Outcomes of haematuria referrals: two-year data from a single large university hospital in Denmark. Scandinavian Journal of Urology 2017; **51**: 282.

28. Church TR, Black C, Aberle DR et al: Results of initial low-dose computed tomographic screening for lung cancer. N Engl J Med 2013; **368**: 1980.

29. Krabbe LM, Svatek RS, Shariat SF et al: Bladder cancer risk: Use of the PLCO and NLST to identify a suitable screening cohort. Urol Oncol 2015; **33**: e19.

30. Georgieva MV, Wheeler SB, Erim D et al: Comparison of the harms, advantages, and costs associated with alternative guidelines for the evaluation of hematuria. JAMA Intern Med. 2019; Epub ahead of print.

31. Ahmed FO, Hamdan HZ, Abdelgalil HB et al: A comparison between transabdominal ultrasonographic and cystourethroscopy findings in adult Sudanese patients presenting with haematuria. Int Urol Nephrol 2015; **47**:223.

32. Ascenti G, Mileto A, Gaeta M et al: Single-phase dual-energy CT urography in the evaluation of haematuria. Clin Radiol 2013; **68**:e87.

33. Bangma CH, Loeb S, Busstra M et al: Outcomes of a bladder cancer screening program using home hematuria testing and molecular markers. Eur Urol 2013; **64**:41.

34. Maheshwari E, O'Malley ME, Ghai S et al: Split-bolus MDCT urography: Upper tract opacification and performance for upper tract tumors in patients with hematuria. AJR Am J Roentgenol 2010; **194**:453.

35. van der Aa MN, Steyerberg EW, Sen EF et al: Patients' perceived burden of cystoscopic and urinary surveillance of bladder cancer: a randomized comparison. BJU Int 2008; **101**:1106.

36. Herr HW: The risk of urinary tract infection after flexible cystoscopy in patients with bladder tumor who did not receive prophylactic antibiotics. J Urol 2015; **193**: 548.

37. Ghandour R, Freifeld Y, Singla N et al: Evaluation of hematuria in a large public health care system. Bladder Cancer 2019; **5**: 119.

38. Blick CGT, Nazir SA, Mallett S et al: Evaluation of diagnostic strategies for bladder cancer using computed tomography (CT) urography, flexible cystoscopy and voided urine cytology: results for 778 patients from a hospital haematuria clinic. BJU Int 2011; **110**: 84.

39. Yecies T, Bandari J, Fam M et al: Risk of radiation from computerized tomography urography in the evaluation of asymptomatic microscopic hematuria. J Urol 2018; **200**:967.

40. Bromage SJ, Liew MP, Moore KC et al: The economic implications of unsuspected findings from CT urography performed for haematuria. Br J Radiol 2012; **85**:1303.

41. Song JH, Beland MD, Mayo-Smith WW: Incidental clinically important extraurinary findings at MDCT urography for hematuria evaluation: prevalence in 1209 consecutive examinations. AJR Am J Roentgenol 2012; **199**:616.

42. Babjuk M, Böhle A, Burger M et al: EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2016. Eur Urol 2017; **71**: 447.

43. Schubert T, Rausch S, Fahmy O et al: Optical improvements in the diagnosis of bladder cancer: implications for clinical practice. Ther Adv Urol 2017; **9**: 251.

44. Lotan Y, Bivalacqua TJ, Downs T et al: Blue light flexible cystoscopy with hexaminolevulinate in non-muscle invasive bladder cancer: review of the clinical evidence and consensus statement on optimal use in the USA – update 2018. Nat Rev Urol 2019; 377.

45. Varshney N, Kebede AA, Owusu-Dapaah H et al: A review of Von Hippel-Lindau Syndrome. J Kidney Cancer VHL 2017; **4**: 20.

46. Pavlovich CP, Walther MM, Eyler RA et al: Renal tumors in the Birt-Hogg-Dube syndrome. Am J Surg Pathol 2002; **12**: 1542.

47. Haas NB and Nathanson KL: Hereditary kidney cancer syndromes. Adv Chronic Kidney Dis 2014; **21**: 81.

48. Yang P, Cornejo KM, Sadow PM et al: Renal cell carcinoma in tuberous sclerosis complex. Am J Sug Pathol 2014; **38**: 895.

49. Clague J, Lin J, Cassidy A et al: Family history and risk of renal cell carcinoma: results from a case-control study and systematic meta-analysis. Cancer Epidemiol Biomarkers Prev 2009; **18**: 801.

50. Daneshmand S, Patel S, Lotan Y et al: efficacy and safety of blue light flexible cystoscopy with hexaminolevulinate in the surveillance of bladder cancer: a phase III, comparative, multicenter study. J Urol 2018; **199**:1158.

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Table 1: Strength of Evidence Definitions

AUA Strength of Evidence Category	GRADE Certainty Rating	Definition
A	High	• We are very confident that the true effect lies close to that of the estimate of the effect
B	Moderate	• We are moderately 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	• Our confidence in the effect estimate is limited • The true effect may be substantially different from the estimate of the effect
	Very Low	• We have very little confidence in the effect estimate • The true effect is likely to be substantially different from the estimate of effect

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

Evidence Grade	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 is 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
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 (Net benefit or harm comparable to other options)	-Benefits=Risks/Burdens -Best action depends on individual patient circumstances -Future Research is 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 -Net benefit (or net harm) comparable to other options -Alternative strategies may be equally reasonable -Better evidence likely to change confidence
Clinical Principle	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	Expert Opinion refers to a statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment.

Table 3: Urothelial Cancer Risk Factors

Risk Factors Included in AUA Microhematuria Risk Stratification System	Additional Urothelial Cancer Risk Factors*
Age	Irritative lower urinary tract symptoms
Male sex	Prior pelvic radiation therapy
Smoking history	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.	

Table 4: AUA Microhematuria Risk Stratification System

Low (patient meets all criteria)	Intermediate (patient meets any one of these criteria)	High (patient 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

Table 5: Known Genetic Renal Tumor Syndromes*

Known genetic renal tumor syndrome
1. **von Hippel-Lindau**
2. **Birt-Hogg-Dube**
3. **Hereditary Papillary Renal Cell Cancer**
4. **Hereditary Leiomyomatosis Renal Cell Cancer**
5. **Tuberous sclerosis**

*The Panel recognizes that this list is not exhaustive.

Microhematuria Evaluation Algorithm

Patient with microhematuria
≥3 RBC/HPF on UA with microscopy

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History and physical exam
Focus on risk factors for urothelial cancer and non-malignant causes[1]

→ Non-malignant or gynecologic source →

Evaluation directed by signs/symptoms
Include urine culture if infection is suspected

Non-malignant or gynecologic source ruled out → **Risk stratification**[1,3]

Non-malignant or gynecologic source identified → **Treat non-malignant or gynecologic source**[4]

Repeat urinalysis positive → **Risk stratification**[1,3]

Treat non-malignant or gynecologic source[4] ↓
Repeat urinalysis positive → **Repeat Urinalysis**
Repeat urinalysis negative → **Release from care**

Risk stratification[1,3] branches:

Low Risk
All of the following:
Women age < 50; Men age < 40 yrs
Never smoker or < 10 pack-years
3-10 RBC/HPF on one UA
No additional risk factors for urothelial cancer[1]
No prior episodes of MH[3]

— Shared decision-making →
Repeat Urinalysis within 6 months OR Cystoscopy and Renal Ultrasound[5]

Intermediate Risk
Any of the following:
Women age 50-59; Men age 40-59 yrs
10-30 Pack-years smoking
11-25 RBC/HPF on one UA
One or more additional risk factors for urothelial cancer[1]
Previously low-risk, no prior evaluation and 3-25 RBC/HPF on repeat UA

↓ **Cystoscopy and Renal Ultrasound**[5]

High Risk
Any of the following:
Women and men age ≥ 60 yrs
>30 Pack-years smoking
> 25 RBC/HPF on one UA
History of gross hematuria
Previously low-risk, no prior evaluation and > 25 RBC/HPF on repeat UA

↓ **Cystoscopy and CT Urogram**[6]

Repeat Urinalysis within 6 months OR Cystoscopy and Renal Ultrasound[5]
Repeat urinalysis negative / Evaluation performed →
Consider Repeat Urinalysis within 12 months
Repeat urinalysis negative → **Release from urologic care**
Repeat urinalysis positive → **Shared decision-making regarding repeat evaluation vs. observation**

Evaluation negative → **Consider Repeat Urinalysis within 12 months**
Evaluation positive → **Treat as indicated**

Treat as indicated
If urologic diagnosis is non-malignant, repeat urinalysis after treatment
Repeat urinalysis positive → **Shared decision-making regarding repeat evaluation vs. observation**
Repeat urinalysis negative → **Release from urologic care**

Shared decision-making regarding repeat evaluation vs. observation
Consider cross-sectional imaging with urography or retrograde pyelograms if not performed previously

↓ **Re-evaluate**
If patient develops gross hematuria, increase in degree of microhematuria or new urologic symptoms

1. Main risk factors for urothelial cancer are those in the AUA risk stratification system (age, male sex, smoking, degree of microhematuria and history of gross hematuria). Additional risk factors for urothelial carcinoma include but are not limited to irritative lower urinary tract voiding symptoms, history of cyclophosphamide or ifosfamide chemotherapy, family history of urothelial carcinoma or Lynch Syndrome, occupational exposures to benzene chemicals or aromatic amines, history of chronic indwelling foreign body in the urinary tract
2. If medical renal disease is suspected, consider nephrologic evaluation, but pursue concurrent risk-based urological evaluation
3. Patients may be low-risk at first presentation with microhematuria, but may only be considered intermediate- or high-risk if found to have persistent microhematuria
4. There are non-malignant and gynecologic sources of hematuria that do not require treatment and/or may confound the diagnosis of MH. Clinicians can consider catheterized urine specimen in women with vaginal atrophy or pelvic organ prolapse. Clinicians must use careful judgment and patient engagement to decide whether to pursue MH evaluation in the setting of chronic conditions that do not require treatment, such as the aforementioned gynecologic conditions, non-obstructing stones or BPH.
5. Clinician may perform cross-sectional imaging with urography or retrograde pyelograms if hematuria persists after negative renal ultrasound
6. MR Urogram or Non-contrast imaging plus retrograde pyelograms if contraindications to CT Urogram