# DIAGNOSIS, EVALUATION and FOLLOW-UP OF ASYMPTOMATIC MICROHEMATURIA (AMH) IN ADULTS: AUA GUIDELINE

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Authors' disclosure of potential conflicts of interest and author/staff contributions appear at the end of the article.

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

**Methods:** A systematic review of the literature using the MEDLINE database (search dates January 1980 – November 2011) was conducted to identify peer-reviewed publications relevant to the diagnosis, evaluation, and follow-up of asymptomatic microhematuria in adults. The review yielded an evidence base of 192 articles after application of inclusion/exclusion criteria. These publications were used to create the majority of the clinical framework. When sufficient evidence existed, the body of evidence for a particular treatment was assigned a strength rating of A (high), B (moderate), or C (low) and evidence-based statements of Standard, Recommendation, or Option were developed. Additional information is provided as Clinical Principles and Expert Opinion when insufficient evidence existed. See text and algorithm for definitions and detailed diagnostic, evaluation, and follow-up information.

**Guideline Statements**

1. Asymptomatic microhematuria (AMH) is defined as three or greater red blood cells (RBC) per high powered field (HPF) on a properly collected urinary specimen in the absence of an obvious benign cause. A positive dipstick does not define AMH, and evaluation should be based solely on findings from microscopic examination of urinary sediment and not on a dipstick reading. A positive dipstick reading merits microscopic examination to confirm or refute the diagnosis of AMH. *Expert Opinion*

2. The assessment of the asymptomatic microhematuria patient should include a careful history, physical examination, and laboratory examination to rule out benign causes of AMH such as infection, menstruation, vigorous exercise, medical renal disease, viral illness, trauma, or recent urological procedures. *Clinical Principle*

3. Once benign causes have been ruled out, the presence of asymptomatic microhematuria should prompt a urologic evaluation. *Recommendation (Evidence Strength Grade C)*

4. At the initial evaluation, an estimate of renal function should be obtained (may include calculated eGRF, creatinine, and BUN) because intrinsic renal disease may have implications for renal related risk during the evaluation and management of patients with AMH. *Clinical Principle*

5. The presence of dysmorphic red blood cells, proteinuria, cellular casts, and/or renal insufficiency, or any other clinical indicator suspicious for renal parenchymal disease warrants concurrent nephrologic workup but does not preclude the need for urologic evaluation. *Recommendation (Evidence Strength Grade C)*

6. Microhematuria that occurs in patients who are taking anti-coagulants requires urologic evaluation and nephrologic evaluation regardless of the type or level of anti-coagulation therapy. *Recommendation (Evidence Strength Grade C)*

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7. For the urologic evaluation of asymptomatic microhematuria, a cystoscopy should be performed on all patients aged 35 years and older. *Recommendation (Evidence Strength Grade C)*

8. In patients younger than age 35 years, cystoscopy may be performed at the physician's discretion. *Option (Evidence Strength Grade C)*

9. A cystoscopy should be performed on all patients who present with risk factors for urinary tract malignancies (e.g., irritative voiding symptoms, current or past tobacco use, chemical exposures) regardless of age. *Clinical Principle*

10. The initial evaluation for AMH should include a radiologic evaluation. Multi-phasic computed tomography (CT) urography (without and with intravenous (IV) contrast), including sufficient phases to evaluate the renal parenchyma to rule out a renal mass and an excretory phase to evaluate the urothelium of the upper tracts, is the imaging procedure of choice because it has the highest sensitivity and specificity for imaging the upper tracts. *Recommendation (Evidence Strength Grade C)*

11. For patients with relative or absolute contraindications that preclude use of multi-phasic CT (such as renal insufficiency, contrast allergy, pregnancy), magnetic resonance urography (MRU) (without/with IV contrast) is an acceptable alternative imaging approach. *Option (Evidence Strength Grade C)*

12. For patients with relative or absolute contraindications that preclude use of multiphase CT (such as renal insufficiency, contrast allergy, pregnancy) where collecting system detail is deemed imperative, combining magnetic resonance imaging (MRI) with retrograde pyelograms (RPGs) provides alternative evaluation of the entire upper tracts. *Expert Opinion*

13. For patients with relative or absolute contraindications that preclude use of multiphase CT (such as renal insufficiency, contrast allergy) and MRI (presence of metal in the body) where collecting system detail is deemed imperative, combining non-contrast CT or renal ultrasound (US) with retrograde pyelograms (RPGs) provides alternative evaluation of the entire upper tracts. *Expert Opinion*

14. The use of urine cytology and urine markers (NMP22, BTA-stat, and UroVysion FISH) is NOT recommended as a part of the routine evaluation of the asymptomatic microhematuria patient. *Recommendation (Evidence Strength Grade C)*

15. In patients with persistent microhematuria following a negative work up or those with other risk factors for carcinoma in situ (e.g., irritative voiding symptoms, current or past tobacco use, chemical exposures), cytology may be useful. *Option (Evidence Strength Grade C)*

16. Blue light cystoscopy should not be used in the evaluation of patients with asymptomatic microhematuria. *Recommendation (Evidence Strength Grade C)*

17. If a patient with a history of persistent asymptomatic microhematuria has two consecutive negative annual urinalyses (one per year for two years from the time of initial evaluation or beyond), then no further urinalyses for the purpose of evaluation of AMH are necessary. *Expert Opinion*

18. For persistent asymptomatic microhematuria after negative urologic work up, yearly urinalyses should be conducted. *Recommendation (Evidence Strength Grade C)*

19. For persistent or recurrent asymptomatic microhematuria after initial negative urologic work-up, repeat evaluation within three to five years should be considered. *Expert Opinion*

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## INTRODUCTION

### Purpose

This guideline's purpose is to provide direction to clinicians and patients regarding how to work up and follow patients with the finding of asymptomatic microhematuria (AMH). The strategies and approaches recommended in this document were derived from evidence-based and consensus-based processes. This document constitutes a clinical strategy and is not intended to be interpreted rigidly. The most effective approach for a particular patient is best determined by the individual clinician and patient. As the science relevant to AMH evolves and improves, the strategies presented here will require amendment to remain consistent with the highest standards of clinical care.

### Methodology

A systematic review was conducted to identify published articles relevant to the diagnostic yield of mass screening for microhematuria (MH) as well as the work-up and follow-up of adult patients with AMH. Literature searches were performed on English-language publications using the MEDLINE database from January 1980 to November 2011. Data from studies published after the literature search cut-off will be incorporated into the next version of this guideline. Preclinical studies (e.g., animal models), pediatric studies, commentary, and editorials were excluded. Review article references were checked to ensure inclusion of all possibly relevant studies. Multiple reports on the same patient group were carefully examined to ensure inclusion of only non-redundant information. The review yielded an evidence base of 192 articles from which to construct a clinical framework for the diagnosis, work-up, and follow-up of AMH.

**Quality of Individual Studies and Determination of Evidence Strength**. Quality of individual studies that were randomized controlled trials (RCTs), controlled clinical trials (CCTs), or comparative observational studies was assessed using the Cochrane Risk of Bias tool.[1] Because there is no widely-agreed upon quality assessment tool for single cohort observational studies, the quality of these studies was not assessed except in the case of diagnostic accuracy studies. Diagnostic accuracy studies were rated using the QUADAS.[2-3]

The categorization of evidence strength is conceptually distinct from the quality of individual studies. Evidence strength refers to the body of evidence available for a particular question and includes consideration of study design, individual study quality, consistency of findings across studies, adequacy of sample sizes, and generalizability of samples, settings, and treatments for the purposes of the guideline. The AUA categorizes body of evidence strength (ES) as Grade A (well-conducted RCTs or exceptionally strong observational studies), Grade B (RCTs with some weaknesses of procedure or generalizability or generally strong observational studies), or Grade C (observational studies that are inconsistent, have small sample sizes, or have other problems that potentially confound interpretation of data).

For some clinical issues, there was little or no evidence from which to construct evidence-based statements. Where gaps in the evidence existed, the Panel provides guidance in the form of *Clinical Principles* or *Expert Opinion* with consensus achieved using a modified Delphi technique if differences of opinion emerged.[4] 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 is no evidence.

**AUA Nomenclature: Linking Statement Type to Evidence Strength.** The AUA nomenclature system explicitly links statement type to body of evidence strength and the Panel's judgment regarding the balance between benefits and risks/burdens.[5] ***Standards*** are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken based on Grade A or Grade B evidence. ***Recommendations*** are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken based on Grade C evidence. ***Options*** are non-directive statements that leave the decision to take an action up to the individual clinician and patient because the balance between benefits and risks/burdens appears relatively equal or appears unclear; ***Options*** may be supported by Grade A, B, or C evidence.

**Limitations of the Literature.** The Panel proceeded with full awareness of the limitations of the MH literature. These limitations included poorly-defined patient groups, heterogeneous patient groups, or patient groups with limited generalizability; use of different AMH work-up thresholds; use of different AMH work-up protocols; failure to follow all patients; and limited follow-up durations. The completed evidence report may be requested from AUA.

**Process.** The Asymptomatic Microhematuria Panel was created in 2009 by the American Urological Association Education and Research, Inc. (AUA). The Practice Guidelines Committee (PGC) of the AUA selected the Panel Chair and Vice Chair who in turn appointed the

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additional panel members with specific expertise in this area.

The AUA conducted a thorough peer review process. The draft guidelines document was distributed to 59 peer reviewers, of which 30 reviewers provided comments. The panel reviewed and discussed all submitted comments and revised the draft as needed. Once finalized, the guideline was submitted for approval to the PGC, and finally to the AUA Board of Directors for final approval. Funding of the panel was provided by the AUA, although panel members received no remuneration for their work.

**Background**

**Definition.** For the purpose of this guideline, microhematuria is defined by the presence of three or more red blood cells (RBCs) per high-powered field (HPF)[6-8] on microscopic examination of one properly-collected, non-contaminated urinalysis with no evidence of infection for which a combination of microscopic urinalysis and dipstick excludes other abnormalities such as pyuria, bacteriuria, and contaminants. In addition, benign causes, such as menstruation, vigorous exercise, viral illness, trauma, and infection, have been excluded.

**Literature Limitations and Interpretation.** The Panel notes that requiring a single positive urinalysis verified by microscopy is a departure from the 2001 AUA Best Practice Statement on asymptomatic microhematuria in adults[9] which required that two of three properly-collected samples be positive on microscopy. The Panel searched for an evidence base to directly support the selection of one, two, or more positive samples as the threshold for evaluation. Such an evidence base would be comprised of studies that used different numbers of positive samples to trigger an evaluation, conducted thorough evaluations, and followed all patients regularly and over long periods of time to determine the impact of requiring one, two, or more positive samples on diagnostic timing, missed diagnoses, and short- and long-term patient outcomes. The existing literature does not contain studies of this type; that is, the literature does not examine the impact of number of positive samples on evaluation yield or patient outcomes.

Therefore, the Panel examined the available literature to determine whether it provided indirect support for the use of one or more positive samples to trigger evaluation. This examination led to the conclusion that one positive sample is sufficient to prompt an evaluation for three reasons. First, there is substantial evidence that microhematuria that is caused by a serious underlying condition such as a malignancy can be highly intermittent;[10-15] therefore, requiring multiple positive samples may result in an undetermined risk of missing a malignant diagnosis.

Second, the existence of this risk is supported by studies that evaluated patients after obtaining one positive sample; urological malignancy rates ranged from 1.0% to 25.8% with most studies detecting malignancies at rates over 2.0%.[11-12, 15-29] A meta-analysis of these studies revealed a pooled urinary tract malignancy rate of 3.3% (95% confidence interval: 2.2 to 5.0%). If previously undiagnosed prostate cancers are included in the meta-analysis, then the pooled overall malignancy rate was 3.6% (95% confidence interval: 2.3 to 5.5%). Therefore, working patients up in response to one positive sample resulted in the detection of significant numbers of life-threatening conditions.

A comparable analysis of studies that required more than one positive sample before undertaking an evaluation[30-41] revealed somewhat lower rates of urinary tract malignancies (1.8% with 95% CI = 1.0 – 3.0%) and all malignancies (1.8% with 95% CI = 1.0 – 3.2%). Whether malignancy detection rates are actually lower in studies that required more than one positive sample, however, is difficult to know given that in a third group of studies it was not clear how many positive samples were required before evaluation.[42-59] Meta-analysis of these studies revealed rates of 4.3% for urinary tract malignancies (95% CI: 3.3 to 5.5%) and 4.8% for all malignancies (95% CI: 3.7 to 6.2%). It is likely that this group of studies includes both those that undertook evaluation after one positive sample as well as those that required more than one positive sample before evaluation. The Panel interpreted these data overall to indicate that evaluation in response to a single positive sample was warranted.

Third, the Panel notes that diagnoses that may not be life-threatening but that would benefit from active clinical management and/or follow up are frequently revealed during the AMH workup. These diagnoses include medical renal disease, calculous disease, benign prostatic enlargement, and urethral stricture. In studies that evaluated patients after one positive sample, rates of calculous disease ranged from 1.0% to 19.4% with a meta-analyzed rate of 6.0% (95% CI: 3.8 – 9.2%), rates of benign prostatic enlargement ranged from 1.0% to 38.7% with a meta-analyzed rate of 12.9% (95% CI: 6.3 – 24.6%), and rates of urethral stricture ranged from less than 1% to 7.1% with a meta-analyzed rate of 1.4% (95% CI: 0.6 – 3.2%). Overall, the Panel interpreted these data regarding possible underlying malignancies as well as other conditions that would benefit from active clinical management to indicate that a single positive sample constitutes AMH and warrants evaluation.*

*Rates of calculous disease andurethral stricture were similar for studies that required more than one positive sample before evaluation and for studies that did not report the number of positive samples required. There were insufficient studies within each of these groups that reported rates of benign prostatic enlargement to allow analysis.

**Prevalence.** The adult population prevalence of microhematuria varies depending on age, gender, frequency of testing, threshold used to define microhematuria, and study group characteristics such as the presence of risk factors (i.e., past or current smoking). Rates of microhematuria using microscopy and dipstick analyses in over 80,000 individuals that participated in health screenings ranged from 2.4% to 31.1%, with higher rates in males over age 60 years and in men who are current or past smokers.[10-15, 17, 19-20, 22-23, 25, 27-28, 60-62] Higher rates are also found in samples that are repeatedly tested.[10-13]

**Origins and Causes.** The origins of microhematuria are either urologic or nephrologic. The most common urological etiologies are benign prostatic enlargement, infection and urinary calculi. Three sets of studies indicate that only a small proportion of patients with microhematuria will ultimately be diagnosed with a urinary tract malignancy. These studies include: Screening studies in which individuals without known health conditions were diagnosed with AMH and worked up; initial work-up studies in which patients who had AMH diagnosed incidentally during a medical encounter such as a check-up were worked up; and further work-up studies in which AMH patients not diagnosed during an initial work-up process were referred on for a specialized work-up. Findings from 17 screening studies revealed an overall urinary tract malignancy rate of approximately 2.6%.[10-15, 17, 19-20, 22-23, 25, 27-28, 60-62] Rates in individual studies ranged from 0% to 25.8%, with repeated testing in high-risk individuals (e.g., male smokers aged 60 years or greater) yielding higher rates. Thirty-two studies reported findings from initial work-ups and reported an overall malignancy rate of 4.0%.[16, 21, 24, 26, 30-32, 34-35, 37, 40-57, 59, 63-66]

Rates in individual studies ranged from 0 to 9.3%. Eight studies reported on AMH patients for whom an initial work-up did not yield a diagnosis and who were referred on for a more detailed work-up; the overall malignancy rate in this group of studies was 2.8%.[58, 60, 67-72] For more detailed discussion of these three sets of studies, see Discussion under Guideline Statement 3. The most common risk factors for urinary tract malignancy in AMH patients are listed in Table 1.[9]

The presence of urinary casts, proteins, and/or dysmorphic red blood cells suggests a medical renal etiology for AMH. Nephropathies and nephritis are the most common causes of microhematuria in this category. The processes may be immunological, infectious or drug-induced. The literature on nephrologic findings in AMH patients is not as extensive as the literature on urological malignancies and the finding of renal malignancy is less common than the finding of bladder malignancy.[73] However, studies report high rates of nephrologic disease in specialized patient groups, including patients with persistent AMH[39, 52, 60, 69, 74-75] and patients referred for a nephrology work up.[31, 48, 76-77] It is important to note that in some studies patients ultimately diagnosed with medical renal disease were younger than age 40 years.[39, 60]

| **Table 1: Common Risk Factors for Urinary Tract Malignancy in Patients with Microhematuria** |
|---|
| Male gender |
| Age (> 35 years) |
| Past or current smoking |
| Occupational or other exposure to chemicals or dyes (benzenes or aromatic amines) |
| Analgesic abuse |
| History of gross hematuria |
| History of urologic disorder or disease |
| History of irritative voiding symptoms |
| History of pelvic irradiation |
| History of chronic urinary tract infection |
| History of exposure to known carcinogenic agents or chemotherapy such as alkylating agents |
| History of chronic indwelling foreign body |

**Evolution of Imaging Technologies.** In the previous version of this document,[9] intravenous urography (IVU) was acknowledged as a mainstay imaging modality for evaluation of the urinary tract because of its widespread availability. The prior document noted, however, that IVU had limited sensitivity in detecting small renal masses and could not distinguish solid from cystic masses, resulting in the need for US, CT or MRI to fully characterize lesions. With regard to US, the authors of the 2001 report noted that although it was excellent for detection of renal cysts, it was limited in detection of small solid renal lesions and urothelial carcinoma in the kidney or ureter. For this reason, in patients with risk factors for serious disease states, the authors of the 2001 report recommended the use of CT urography.

A decade later, this Panel approached the issue of appropriate evaluation of the AMH patient with the goal of identifying the imaging strategy that creates maximum diagnostic certainty without the need for additional imaging procedures in order to minimize patient burden and the possibility of missed diagnoses.

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US and IVU generate criteria identifying morphologic changes in the kidneys and collecting system, but while the presence of masses is established with reasonable accuracy, these methods do not provide criteria for tissue characterization. Therefore, the use of these modalities does not exclude the need for additional imaging studies. In addition, the sensitivities and specificities of US and IVU are such that the possibility of missed diagnoses is significant (see discussion under Guideline Statement 10). Both of these issues are avoided with the use of CT urography and MRI urography – two modalities that have been developed and refined during the decade since the publication of the prior document.[78] CT urography provides a detailed anatomic depiction of the urinary tract. MR urography, although potentially providing less anatomic detail, has the advantage of avoiding the use of ionizing radiation. Both modalities are superior to IVU and US in sensitivity and specificity for a wide variety of urologic conditions detectable in the AMH patient.[78] For these reasons, the Panel emphasizes use of these modalities in the diagnosis sections that follow.

It is important to note, however, that the choice of imaging modality is best made by the treating physician who has full knowledge of a particular patient's history and in the context of available resources. In addition, the Panel is fully aware that in patients with contraindications for use of CT and/or MRI, the combination of US with retrograde pyelograms may be the optimal imaging strategy.

**Diagnosis and Work-Up**

**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.

Male patients: Mid-stream 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 the obese female patient 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 present in the bladder or only results from 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.

**Microscopy Technique.** Ten ml aliquots from a freshly voided clean-catch mid-stream urine specimen should be centrifuged in 15 ml tubes at 2,000 revolutions per minute for 10 minutes (or 3,000 revolutions per minute for 5 minutes)[79] immediately after collection. The supernatant should be poured off, and the sediment resuspended in 0.3 ml supernatant and/or saline, placed on a microscopic slide (75 mm x 25 mm) and covered with a cover slip (22 mm x 22 mm). At least 10-20 microscopic fields should be examined under 400x magnification. Three or more red blood cells (RBCs) per field is considered a positive specimen.[10, 79-81]

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.[82-83] 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.[84]

The panel emphasizes that a positive dipstick merits microscopic examination of the urinary sediment as described, but does not warrant full evaluation unless this confirms there are three or greater RBC/HPF. If this is not the case but the clinician is suspicious that the findings could reflect true AMH, then repeat microscopic testing may be reasonable after assessing risks of the clinical presentation.

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**Diagnostic and Work-up Framework**

The guideline statements below are organized to follow and provide the rationale for the accompanying algorithm.

| Table 2: AUA Nomenclature Linking Statement Type to Evidence Strength |
|---|
| **Standard:** Directive statement that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be taken based on Grade A or B evidence |
| **Recommendation:** Directive statement that an action should (benefits outweigh risks/ burdens) or should not (risks/burdens outweigh benefits) be taken based on Grade C evidence |
| **Option:** Non-directive statement that leaves the decision regarding an action up to the individual clinician and patient because the balance between benefits and risks/burdens appears equal or appears uncertain based on Grade A, B, or C evidence |
| **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 |

**Guideline Statement 1.**

**Asymptomatic microhematuria (AMH) is defined as three or greater RBC/HPF on a properly collected urinary specimen in the absence of an obvious benign cause. A positive dipstick does not define AMH, and evaluation should be based solely on findings from microscopic examination of urinary sediment and not on a dipstick reading. A positive dipstick reading merits microscopic examination to confirm or refute the diagnosis of AMH.** ***Expert Opinion***

**Discussion.** The Panel emphasizes that the diagnosis of AMH should be based on findings from microscopic examination of urinary sediment as described under **Microscopy Technique** above. A positive dipstick is not sufficient to substantiate an AMH diagnosis. Patients who have a positive dipstick test but a negative specimen on microscopy should have three additional repeat tests. If at least one of the repeat tests is positive on microscopy, then workup should be undertaken. If all three specimens are negative on microscopy, then the patient may be released from care.

**Guideline Statement 2.**

**The assessment of the asymptomatic microhematuria patient should include a careful history, physical examination, and laboratory examination to rule out causes of AMH such as infection, menstruation, vigorous exercise, medical renal disease, viral illness, trauma, or recent urological procedures.** ***Clinical Principle***

**Discussion.** Evaluation of the AMH patient should include a careful history and physical examination, including assessment of blood pressure. There are many causes of AMH that do not require a full diagnostic work-up, including vigorous exercise, presence of pre-existing medical renal disease, presence of infection or viral illness, present or recent menstruation, exposure to trauma, or recent urological procedures (e.g., catheterization). The AMH patient should be queried regarding these potential causes of AMH, treated as appropriate and re-tested once the condition has resolved. The Panel notes that in complex patients, such as those with a known underlying benign cause of AMH (e.g., asymptomatic stones, catheterization), the risk for concurrent disease remains and these patients should be evaluated periodically at clinician discretion (see Guideline Statements 16 and 17).

**Guideline Statement 3.**

**Once benign causes have been ruled out, the presence of asymptomatic microhematuria should prompt a urologic evaluation.** ***Recommendation***

**Discussion.** ***(Evidence strength – Grade C; Benefits outweigh risks/burdens).*** A small percentage of individuals diagnosed with AMH will ultimately be determined to have a urinary tract malignancy requiring intervention. Three sets of studies support this statement: Screening studies in which individuals without known health conditions were diagnosed with AMH and worked up; initial work-up studies in which patients who had AMH diagnosed incidentally during a medical encounter such as a check-up were worked up; and further work-up studies in which AMH patients not diagnosed during an initial work-up process were referred on for a specialized work-up. Seventeen screening studies reported on diagnostic

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findings for approximately 3,762 AMH individuals;[10-15, 17, 19-20, 22-23, 25, 27-28, 60-62] 98 individuals were diagnosed with a urinary tract malignancy for an overall rate of 2.6%. Rates in individual studies ranged from 0% to 25.8%, with repeated testing in high-risk individuals (e.g., male smokers aged 60 years or greater) yielding higher rates. Thirty-two studies conducted initial work-ups on 9,206 AMH patients;[16, 21, 24, 26, 30-32, 34-35, 37, 40-57, 59, 63-66] 368 patients were diagnosed with a malignancy for an overall rate of 4.0%. Rates in individual studies ranged from 0 to 9.3%. Eight studies reported on 1,475 AMH patients for whom an initial work-up did not yield a diagnosis and who were referred on for a more detailed work-up;[58, 60, 67-72] 41 individuals were ultimately diagnosed with a urinary tract malignancy for an overall rate of 2.8%.

In addition, other conditions that would benefit from active clinical management were frequently diagnosed. For example, rates of calculous disease ranged from 1.4% to 25.6% with most studies reporting rates above 5.0%. Rates of benign prostatic enlargement ranged from less than 1.0% to 47.1% with nearly half of the studies reporting rates greater than 10.0%. Urethral stricture rates ranged from less than 1% to 7.1% with more than one-third of studies reporting rates of greater than 2.0%. Overall, the Panel interpreted these data to indicate that the frequency of underlying conditions that may be life-threatening or that may benefit from intervention and/or management was sufficient to warrant an evaluation.

As a group, these studies constitute Grade C evidence because most were single cohort observational designs and there was considerable variability across studies in patient characteristics, work-up protocols, and follow-up durations. The Panel notes that there is a critical knowledge base gap regarding AMH. In particular, studies of AMH and the diagnostic yield associated with AMH in patients that have been thoroughly worked up and carefully followed for long periods of time and that can be stratified based on age, gender, and other putative risk factors are greatly needed. In the absence of this information, distinguishing among patient subgroups for the purpose of differential work up protocols is accompanied by high levels of uncertainty. Given the state of the available literature, the Panel judged that the benefit of detecting and treating a life-threatening urinary tract malignancy or other condition that would benefit from intervention or management outweighed the risks/burdens associated with a urologic evaluation.

**Guideline Statement 4.**

**At the initial evaluation, an estimate of renal function should be obtained (may include calculated eGFR, creatinine, and BUN) because intrinsic renal disease may have implications for renal related risk during the evaluation and management of patients with AMH.** ***Clinical Principle***

**Discussion.** Renal function has implications for interpreting hematuria in the presence or absence of intrinsic renal disease and implications for renal related risk in the evaluation and management of patients with hematuria. Abnormal renal function warrants evaluation to include establishing the etiology of renal dysfunction either as it relates to, or independent of, the cause of hematuria. Furthermore, renal dysfunction increases the risk of contrast or gadolinium radiologic studies and needs to be considered in the selection of these diagnostic procedures. In addition, if procedures are considered for the treatment of urologic diseases that may result in a reduction in renal function, then the implications of this reduction may be more pronounced for patients who have baseline abnormal renal function. Concurrent nephrologic evaluation and a clear understanding of nephrologic factors should be considered in the patient with either urinary abnormalities suggestive of nephrologic disorders or in the patient with abnormal renal function.

**Guideline Statement 5.**

**The presence of dysmorphic red blood cells, proteinuria, cellular casts, and/or renal insufficiency or any other clinical indicator suspicious for renal parenchymal disease warrants concurrent nephrologic workup but does not preclude the need for urologic evaluation.** ***Recommendation***

**Discussion.** ***(Evidence strength – Grade C; Benefits outweigh risks/burdens).*** A small percentage of individuals diagnosed with AMH will ultimately be determined to have a nephrologic condition requiring intervention. The presence of dysmorphic red blood cells (RBCs) detected by conventional microscopy, phase-contrast microscopy, or automated analyzer exhibits too broad a range of sensitivities (from 31.9% to 100%) and specificities (from 33.3% to 100%) to be used as a sole indicator of glomerular causes of microhematuria.[85-115] However, the presence of dysmorphic RBCs can be helpful in the context of other clinical information (e.g., patient history, physical exam, laboratory data such as proteinuria or renal dysfunction) in directing the evaluation toward glomerular causes of hematuria.

Although the presence of dysmorphic RBCs suggests a glomerular process, this finding does not exclude the potential for urologic processes, and evaluation for urologic causes should be conducted based on the presence of co-existing risk factors and clinical findings

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suggestive of urologic disease. In addition, the presence of proteinuria or renal insufficiency should prompt evaluation for nephrologic diseases in the microhematuria patient regardless of RBC morphology findings. In this setting also, the presence of renal disease does not exclude a urologic process and evaluation should include assessment for urologic pathology based on the presence of microhematuria and patient characteristics summarized in these recommendations.

Evidence strength is Grade C because most of the available studies were single cohort observational designs and there was considerable variability across studies in patient characteristics, work-up protocols, and follow-up durations. In addition, for the dysmorphic RBC studies, there was variability in the criterion for a positive test, in the criterion for glomerular disease, in sample preparation, and in reference standards.

**Guideline Statement 6.**

**Microhematuria that occurs in patients who are taking anti-coagulants requires urologic evaluation and nephrologic evaluation regardless of the type or level of anti-coagulation therapy.** ***Recommendation***

**Discussion.** ***(Evidence strength – Grade C; Benefits outweigh risks/burdens).*** Culclasure[116] followed patients on anti-coagulation therapy (mean age 65 years) and a control group of patients not on anti-coagulation therapy (mean age 63.7 years). The criterion for diagnosis of AMH was ≥ 5 RBCs/HPF at least twice during monthly tests for two years. Of the 69 patients in the anti-coagulation group, 32 manifested AMH (46.4%); 11 of 30 controls manifested AMH (36.7%). Among the 32 AMH anti-coagulation patients, one renal cancer and one bladder cancer were diagnosed. Among the 11 AMH control patients, one bladder cancer was diagnosed. When data were analyzed as patient-months to take into account varying levels of anti-coagulation across patients and within individual patients over time, there was no difference in the number of microhematuria episodes between anti-coagulation patients and controls and no relationship between level of anti-coagulation and microhematuria episodes.

The Panel interpreted these data to indicate that work-up for urinary tract and nephrologic abnormalities is indicated in patients on anti-coagulation therapies including warfarin, antiplatelet agents, aspirin, and injectable agents such as heparin and heparin derivatives. The evidence strength for this statement is Grade C because it is based on one comparative observational study with a small sample size. The Panel also notes it should not be assumed that other groups of patients with a known potential cause of AMH, such as those with a chronic indwelling catheter or those using intermittent catheterization, do not need evaluation. At the judgment of the treating clinician, these patients also may require workup to rule out other causes of AMH.

**Guideline Statement 7.**

**For the urologic evaluation of asymptomatic microhematuria, a cystoscopy should be performed on all patients aged 35 years and older.** ***Recommendation***

**Discussion.** ***(Evidence strength – Grade C; Benefits outweigh risks/burdens).*** The evidence reviewed under Guideline Statement 2 was used to support this statement. Among the 98 individuals diagnosed with a urinary tract malignancy in the screening studies, 95 individuals (97%) were older than age 35 years. Among the 409 patients diagnosed with a urinary tract malignancy in the initial and further work-up studies, 406 (99.3%) were older than age 35 years. The Panel interpreted these data to indicate that cystoscopy should be performed in individuals aged 35 years and older. Infectious risk of cystoscopy is low, and the Best Practice Policy Statement on Urologic Surgery Antimicrobial Prophylaxis (2008)[117] specifically recommends against routine use of antibiotics for routine cystoscopy. The evidence strength is Grade C because most studies were single cohort observational designs and there was considerable variability across studies in patient characteristics, work-up protocols, and follow-up durations.

**Guideline Statement 8.**

**In patients younger than age 35 years, cystoscopy may be performed at the physician's discretion.** ***Option***

**Discussion.** ***(Evidence strength – Grade C; Balance between benefits and risks/burdens unclear).*** The probability of a urinary tract malignancy in patients younger than age 35 years is extremely low. In the literature reviewed to support Guideline Statements 1 and 4, approximately 1.2% of patients (6 of 504) diagnosed with a urinary tract malignancy were younger than age 35 years. In younger patients, the physician should be guided by the results of the history and physical and other clinical indicators to determine whether a cystoscopy is in the best interests of the patient. Evidence strength is Grade C because most studies were single cohort observational designs and there was considerable variability across studies in patient characteristics, work-up protocols, and follow-up durations.

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**Guideline Statement 9.**

**A cystoscopy should be performed on all AMH patients who present with risk factors for urinary tract malignancies (e.g., history of irritative voiding symptoms, current or past tobacco use, chemical exposures) regardless of age.** ***Clinical Principle***

**Discussion.** Accepted risk factors for significant underlying urinary tract disease include current or past tobacco use, history of pelvic irradiation, alkylating chemotherapeutic agents such as cyclophosphamide, and exposure to occupational hazards such as dyes, benzenes, and aromatic amines. All patients with risk factors should have a cystoscopy regardless of age.

**Guideline Statement 10.**

**The initial evaluation for AMH should include a radiologic evaluation. Multi-phasic computed tomography (CT) urography (without and with IV contrast), including sufficient phases to evaluate the renal parenchyma to rule out a renal mass and an excretory phase to evaluate the urothelium of the upper tracts, is the imaging procedure of choice because it has the highest sensitivity and specificity for imaging the upper tracts.** ***Recommendation***

**Discussion.** ***(Evidence strength – Grade C; Benefits outweigh risks/burdens).*** The ideal radiologic evaluation for AMH would present minimal risk while providing sufficient diagnostic information in a single imaging session to identify disorders requiring treatment and/or follow-up or referral and to rule out rare but serious diseases without the need for repeat scans or additional studies. This imaging strategy maximizes certainty for the clinician and the patient regarding potential causal factors for AMH in a timely manner and fully informs the treatment plan. The literature indicates that less than 1% of AMH patients who had negative findings after a thorough workup manifested a serious disease state during 14 years of follow-up[118] reinforcing the importance of completing an initial workup that provides maximal diagnostic certainty. CT urography meets these criteria; other imaging strategies (i.e., US in combination with intravenous pyelograms) do not meet these criteria.[78] Further, the American College of Radiology gave CT urography its highest rating for appropriateness in the work up of hematuria patients and notes that the scan must include use of high-resolution imaging during the excretory phase.[119]

**Challenges in Interpreting the Literature.** The literature on imaging to work up patients diagnosed with AMH is limited and provided insufficient information across imaging modalities; therefore, the Panel also considered the broader imaging literature in support of this recommendation. The Panel is fully aware that in clinical practice, it is common to stratify patients based on known risk factors for malignancy and other conditions and to conduct more rigorous radiological evaluations on patients with risk factors (e.g., past or current smoking, older age). The Panel searched for evidence that would support this practice in the asymptomatic microhematuria patient for whom benign causes have been excluded. Ideally, such an evidence base would be comprised of studies in which patients were risk-stratified and then patients in each risk category were worked up according to different protocols and followed to determine the impact of protocol on findings and patient outcomes. No studies of this type were retrieved. Finding indirect evidence to justify differential evaluation based on risk stratification in the AMH patient also was problematic. Key information regarding the prevalence of AMH stratified by risk factors is not in the literature. Although increased risk for malignancy is associated with increasing age and tobacco use, for example, the proportion of patients with malignancies and other diagnoses who present with AMH also is not known. In addition, studies that discussed the risk factor status of patient subgroups (i.e., of smokers, of older patients) rarely reported findings separately for risk subgroups. Given the lack of an evidence base to support a differential radiological evaluation in AMH patients with different risk profiles, and the possibility of obtaining a diagnosis requiring prompt clinical action even in patients who may not have risk factors, the Panel judged that radiological evaluation is necessary in all AMH patients and multi-phasic CTU is preferred because of its high sensitivity and specificity. The Panel emphasizes that this recommendation is not intended to replace the judgment of the physician faced with a particular patient and leaves the ultimate choice of imaging modality up to the treating physician who best knows that patient and his/her history, preferences, and values. In some low-risk patients, particularly those younger than 35 years without risk factors in whom the risk of a malignancy is extremely small, a more limited or alternative evaluation may be sufficient.

**Multi-phasic CT Urography.** Multi-phasic CT urography with and without contrast had the most consistent and highest sensitivities and specificities for detecting lesions of the renal parenchyma and the upper tracts (e.g., most reported values at 90% or above).[34, 58, 71, 120-135] The multi-detector CT (MDCT) scan appears to offer optimal imaging information.[78]

In particular, MDCT technology makes possible a much faster rate of recording than single detector CT. Thus, the various phases of contrast transit are better defined and are without artifacts caused by overlapping phases.

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Four distinct phases are the goal: 1) a pre-enhancement phase to establish baseline densities of tissues and high or variable densities such as calculi, hematomas or fat-containing structures; 2) an arterial phase identifying neoplastic or inflammatory neovascularity; 3) a cortico-medullary or parenchymal phase defining evidence of renal parenchymal changes and equating it to sustained damage; and 4) an excretory phase which demonstrates the collecting system, ureters and bladder and any abnormalities affecting the urothelium. The CT urogram can be generated from single detector or MDCT with added 3D and volume rendering reconstructions of the excretory phase, and hence is particularly useful to assess urothelial abnormalities of the ureter. To minimize radiation exposure of the patient, low x-ray tube voltage (kV), high current exposure time product (mAs), and adaptive statistical iterative reconstruction algorithm (ASIR) settings are advocated.[136] Field limitation to the area of interest and shielding of thyroid and sternum are recommended. It should be noted that CTU provides better detail definition of morphology than does MRU. The panel notes that in younger patients the upper tract urothelial phase may not be necessary; this decision is best made by the treating clinician. In addition, the use of IV contrast material may be contraindicated in some patients with renal insufficiency and alternative imaging strategies may be appropriate (see discussion below and under Guideline Statements 11, 12 and 13).

The use of iodinated contrast is a well-known cause of acute renal failure, especially in patients with impaired renal function.[137-139] The risks of severe contrast reactions using American College of Radiology (ACR) criteria, however, are extremely low. ACR defines reactions as mild (no treatment required other than anti-histamines), moderate (requiring treatment with additional substances and close monitoring), or severe (life-threatening reaction requiring urgent treatment and possibly hospitalization). In a review of 18 studies reporting outcomes for 261,657 patients,[140-157] only four deaths were reported (two with unspecified ionic agents, one with iopromide and one with meglumine) and only 38 other severe reactions occurred. Mild and moderate reactions were common, ranging from 0% to 50.8% of patients but studies varied widely in how patients were queried about reactions and in the interval over which they were queried (e.g., ranging from 30 min post-scan to a week post-scan).

For some reported options that may reduce contrast nephropathy risk, such as N-acetyl cysteine administration, a nephrologist may be helpful in weighing options, identifying measures that may mitigate the risks, as well as in providing input that may help with imaging modality selection. The level of renal dysfunction is preferably determined from estimates of the glomerular filtration rate (GFR) rather than using the serum creatinine or blood urea nitrogen (BUN) since GFR better predicts risk. Among the available strategies, hydration, either intravenous or oral, is recommended for contrast risk reduction in patients with renal insufficiency. For detailed protocols, see American College of Radiology *Manual on Contrast Media, Version 7* (ACR 2010).

A history should be obtained from all patients with regard to prior contrast administration and potential allergic reactions. In addition, the Panel suggests that consideration for pre-medication with steroids be given to patients with a documented history of contrast reaction. One generally accepted protocol for corticosteroid prophylaxis consists of prednisolone 30 mg orally to be given 12 and 2 hours before contrast medium (preferably non-ionic) administration. An alternate technique is administration of a prednisolone 30 mg 24 hours and 6 hours prior to contrast exposure. Corticosteroids are not effective if the initial dose is given less than 6 hours before contrast medium administration. In patients with marginal renal function as determined by GFR, pre-hydration with 1000 ml 5% glucose should be considered. For more detailed information on contrast allergy prophylaxis, see the ACR *Manual on Contrast Media, Version 7* (ACR 2010). In addition, a crash cart with resuscitation drugs and equipment needs to be available.

**Less Optimal Imaging Strategies**. Ultimately, the choice of the imaging strategy for a particular patient is best made by the treating clinician with full knowledge of that patient's history and preferences and of the resources available in the clinical context. The Panel's priority in selecting the optimal imaging strategy of multi-phasic CTU was to maximize diagnostic certainty and the opportunity for prompt clinical action if warranted, to minimize the patient burden associated with anxiety regarding an uncertain diagnosis and the need to obtain additional tests, and to minimize the risk of missing serious disease states. The Panel is aware, however, that US, either alone or in combination with IVU, is widely-used in clinical practice and is recommended by other guidelines (e.g., Wollin 2009). The use of US alone, or in combination with IVU, is an alternative but less optimal option for imaging because these techniques do not reliably produce diagnostic certainty. Certainty is compromised by the fact that indeterminant findings will require the use of additional imaging techniques and by the more serious issue that lesions or clinical conditions requiring prompt action may be missed entirely.

Interpreting the US and IVU literature is complicated by the fact that patient characteristics vary across studies and the diagnostic focus for which sensitivity and specificity was calculated also varied (e.g.,

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malignancies, stones, only bladder lesions, only upper tract lesions, all diagnoses, etc.). Sensitivity values exhibit a wide range, suggesting inconsistent results across studies, but the values reported in most studies are relatively low for these modalities, resulting in false negative rates that present a clinically relevant probability of a missed diagnosis.

For example, in 158 patients worked up for either micro - or macrohematuria, US had a sensitivity of 67.3% for all malignancies, 100% for renal malignancies, and 50% for upper tract TCC.[47] Edwards[49] reported in a group of 73 patients that US had a sensitivity of 95.8% for all upper tract malignancies (renal and ureteral), 100% for renal malignancies, but only 76.9% for upper tract TCC (failing to detect three TCC). Insufficient information was provided in these two studies to calculate specificities, and it should be noted that others have reported that US has poor sensitivity for small renal masses (e.g., Jamis-Dow 1996). In a study of 297 patients (from which patients known to have stones or bladder malignancies were excluded), US had a sensitivity of 55.6% (failing to detect four of nine upper tract tumors) and a specificity of 94.4% for upper tract malignancies.[161] IVU also was performed in this study and exhibited sensitivity of 66.7% and specificity of 91.3% for upper tract malignancies. El-Galley[32] reported that US had a sensitivity of 50% and specificity of 95% for malignancies plus stones compared to IVU which exhibited 38% sensitivity and 90% specificity and CT which exhibited 92% sensitivity and 93% specificity.

A small group of studies focused on the use of IVU in hematuria patients (both micro-and macrohematuria). Albani[120] reported in two different groups of patients that IVU had 60% sensitivity for renal malignancies (insufficient information provided to calculate specificity) compared to MDCT urography which had 100% sensitivity for renal malignancies (approximately 250 patients in each group). Gray-Sears[34] reported in 115 patients (all with microhematuria) that IVU had a sensitivity of 60.5% for all diagnoses (benign and malignant) and a specificity of 90.9% compared to three-phase helical CT which had a sensitivity of 100% and a specificity of 97.4%. In 91 patients who had IVU and then helical CT after IVU without additional contrast, IVU sensitivity was 68.2% for all diagnoses (benign and malignant) and 66.7% for malignancies and stones compared to helical CT which had 81.8% sensitivity for all diagnoses and 83.3% sensitivity for malignancies and stones. Specificity for all diagnoses was 95.7% for IVU and 97.1% for helical CT. In addition, a recent systematic review and meta-analysis confirmed the superior imaging characteristics of CTU compared to IVU, reporting pooled values for CTU sensitivity of 96% and for specificity of 99%.[162]

The Panel interpreted these data to indicate that the use of US with or without IVU presents significant risks for missed diagnoses. Although serious findings are rare in the AMH patient, and particularly in younger AMH patients and in patients without risk factors, they have been reported, and their presence requires a prompt clinical response. Therefore, the Panel judged that use of these modalities is an alternative, but less optimal imaging strategy.

Evidence strength is Grade C because of heterogeneous patient groups, the relative lack of studies in AMH patients, and the fact that most studies were single cohort observational designs. In addition, for the contrast reaction studies, there was great variability in how patients were queried regarding reactions and in follow-up duration (e.g., from 30 min post-scan to one week post-scan).

**Guideline Statement 11.**

**For patients with relative or absolute contraindications that preclude use of multi-phasic CT (such as renal insufficiency, iodinated contrast allergy, pregnancy), magnetic resonance urography (MRU) (without/with intravenous contrast) is an acceptable alternative imaging approach. *Option***

**Discussion. *(Evidence strength – Grade C; Balance between benefits and risks/burdens unclear).*** In patients with renal insufficiency or history of iodinated contrast allergy or in the pregnant patient, MRU is an alternative imaging option. It should be noted that although there are potential safety advantages to the use of MRU in patients with a history of iodinated contrast reaction or other contraindication to multi-phasic CTU, its role in working up AMH patients is unclear given the lack of literature in this population. In addition, there appears to be variability in access to high quality MRU technology and lack of standardization of protocols. Further, although MRU appears to provide high sensitivity/specificity imaging of the renal parenchyma, its role in visualizing collecting system detail is indeterminate.[163-165]

Nevertheless, MRU can provide relative diagnostic certainty regarding some underlying causes of AMH. For example, its accuracy in identifying renal obstructions is similar to CTU.[166-168] In the pregnant female, MRU allows distinguishing physiologic dilatation of the right ureter from an obstructive uropathy caused by a calculus without use of IV contrast.[169-171] Sensitivity for detecting renal lesions is reported to be higher than 90%.[125, 133, 173-175] With gadolinium enhancement, sensitivity for upper tract malignancies has been reported to be as high as 80%.[175] The risk of contrast reaction to gadolinium (nephrogenic systemic

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fibrosis) in patients with renal insufficiency is uncertain but may be severe in some patients with advanced renal insufficiency. If there is abnormal renal function, then a nephrologist may be helpful to assess the risk from gadolinium.

Therefore, the Panel judged that the use of MRU is an alternative imaging strategy that can provide relatively high diagnostic certainty in patients who cannot undergo CTU. As with all imaging decisions, this decision is best made by the individual physician who is fully informed regarding a particular patient's history and associated clinical conditions as well as available imaging resources.

Evidence strength is Grade C given the lack of studies in AMH patients, the heterogeneous patient groups, and the weak study designs of the available studies.

**Guideline Statement 12.**

**For patients with relative or absolute contraindications that preclude use of multi-phasic CT (such as renal insufficiency, iodinated contrast allergy, pregnancy) where collecting system detail is deemed necessary, combining magnetic resonance imaging (MRI) with retrograde pyelograms (RPGs) provides alternative evaluation of the entire upper tracts. *Expert Opinion***

**Discussion.** Retrograde pyelograms (RGPs) are a safe way to evaluate the entire urothelium for filling defects, obstructions, or irregularities in the patient who is not a candidate for CTU or MRU. Although invasive, RGP allows confirmation of the radiologic diagnosis while also confirming the need for uretero-renoscopy or upper tract sampling. The combination of RPGs with MRI can provide an adequate upper tract evaluation for the purpose of clinical decision-making in the patient who cannot tolerate CTU or MRU.

Ultimately, decisions regarding imaging strategy in high-risk patients are best made by the treating clinician who has detailed knowledge regarding a given patient's history and current circumstances and the availability of imaging options in the clinical setting. In some circumstances, non-contrast CT or renal ultrasound in combination with RPGs may provide sufficient information to guide clinical care and may be the best choices in patients with compromised renal function who also have contraindications to MRI (e.g., a pacemaker; see Guideline Statement 13). In general, the Panel does not advocate the routine use of RPGs, but in the special circumstances described above, their use may be appropriate.

**Guideline Statement 13.**

**For patients with relative or absolute contraindications that preclude use of multi-phasic CT (such as renal insufficiency, iodinated contrast allergy) and MRI (such as presence of metal in the body) where collecting system detail is deemed necessary, combining non-contrast CT or renal ultrasound with retrograde pyelograms (RPGs) provides alternative evaluation of the entire upper tracts. *Expert Opinion***

**Discussion.** Some AMH patients will present with contraindications to CTU, MRU, and MRI. In this clinical scenario, combining non-contrast CT or US with retrograde pyelograms provides an alternative evaluation of the upper tracts. The Panel notes that non-contrast CT will provide more information and create greater diagnostic certainty than will US. For certain patients such as the pregnant female, however, only US in combination with RPGs should be used (see section titled Special Considerations in the Pregnant Female).

**Special Considerations in the Pregnant Female**

The pregnant female AMH patient requires special consideration. The majority of AMH cases are associated with non-life threatening conditions and less than 5% are associated with malignancy. Further, the incidence of AMH in pregnant and non-pregnant women is similar (approximately 4%.[176] Brown[177] reported that women with and without AMH during pregnancy had offspring of similar birth weight and gestational age at delivery, and similar rates of gestational hypertension and pre-eclampsia. Given that malignancies in this low risk group (typically < 40 years of age) are rare, the Panel recommends use of MRU, MRI with RPGs, or ultrasound to screen for major renal lesions with a full workup after delivery once gynecological bleeding and persistent infection have been ruled out.

**Guideline Statement 14.**

**The use of urine cytology and urine markers (NMP22, BTA-stat, and UroVysion FISH) is NOT recommended as a part of the routine evaluation of the asymptomatic microhematuria patient. *Recommendation***

**Discussion. *(Evidence strength – Grade C; Risks/ burdens outweigh benefits).*** The literature on urine cytology and urine markers indicates that these tests lack sufficient clinical reliability to be used in the routine evaluation of the AMH patient. Twenty-five studies reported sensitivity and/or specificity values for urine cytology.[25-26, 32, 36, 42, 53, 59, 65, 178-194] Sensitivity values ranged from 0% to 100%; specificity values ranged from 62.5% to 100%. Twelve studies reported sensitivity and specificity values for detection of urinary tract malignancies for various urine markers.[25, 179, 186-

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[195] For NMP22, sensitivities ranged from 6.0% to 100% and specificities ranged from 62% to 92%. Only two studies reported on BTA-stat[192-193] and only specificities could be calculated (69% and 73%, respectively) because no malignancies were detected in the samples. Three studies reported on UroVysion FISH;[25, 191-192] sensitivities ranged from 61% to 100% and specificities ranged from 71.4% to 93%. Overall, the Panel interpreted these data to indicate that these tests are not appropriate for routine use in AMH patients because the burden of emotional stress that could result from a false positive test and the risks of unnecessary diagnostic procedures (e.g., biopsies) outweighed the potential benefits to the patient. Evidence strength is Grade C because of lack of sufficient sample information, heterogeneous samples with potential poor generalizability to the AMH patient, lack of procedural detail, and the heterogeneity of findings across studies. In addition, most studies were single cohort observational designs.

**Guideline Statement 15.**

**In patients with microhematuria present following a negative work up or those with other risk factors for carcinoma in situ (e.g., irritative voiding symptoms, current or past tobacco use, chemical exposures), cytology may be useful. *Option*.**

**Discussion.** ***(Evidence strength – Grade C; Balance between benefits and risks/burdens uncertain).*** Although urine cytology exhibits inadequate reliability as a clinical indicator for malignancy when used as a single test, it can be useful in the context of the high-risk patient in conjunction with other findings suggestive of malignancy. The literature review indicated sensitivity values that ranged from 0% to 100% and specificity values that ranged from 62.5% to 100% (see Statement 12 discussion). However, of the 22 values reported for specificity, 18 were 90% or greater. These data suggest that although cytology is likely to result in a false negative finding, it is unlikely to produce a false positive finding. The decision to incorporate cytology as part of the AMH work-up is best made by the treating physician who has knowledge of the patient's history, physical findings, and other clinical information. It should be emphasized, however, that a negative cytology finding does not preclude a full work-up. Use of urine markers is not recommended (see Discussion under Guideline Statement 14). Evidence strength is Grade C because of the predominance of single cohort observational designs, lack of sufficient sample information, heterogeneous samples with potential poor generalizability to the AMH patient, lack of procedural detail, and the heterogeneity of findings across studies.

**Guideline Statement 16.**

**Blue light cystoscopy should not be used in the evaluation of patients with asymptomatic microhematuria. *Recommendation***

**Discussion.** ***(Evidence strength – Grade C; Risks/ burdens outweigh benefits).*** Blue light cystoscopy is a form of fluorescence cystoscopy in which a photosensitizing compound is instilled in the bladder where it binds preferentially with neoplastic cells and emits visible fluorescence under blue-violet illumination).[196] Eighteen papers reported findings of conventional white-light cystoscopy compared to blue-light cystoscopy for 2,233 patients (1,605 patients were evaluated with 5-aminolaevulinic acid, ALA; 628 patients were evaluated with hexyl aminolevlinate, HAL)[197-214]. All studies were conducted in bladder cancer patients, limiting generalizability to AMH patients. Sensitivities of white light cystoscopy ranged from 17.3% to 83.2%; specificities ranged from 66.4% to 93%. For the ALA studies, sensitivities ranged from 86.5% to 98.3%; specificities ranged from 35% to 65%. For the HAL studies, sensitivities ranged from 76% to 97%; specificities ranged from 61% to 95%.

Both ALA and HAL, as well as the associated blue light equipment, are FDA-approved for evaluation of patients with suspicion of papillary bladder cancer. While most reported adverse events have been minor, there are reports of anaphylactoid shock, hypersensitivity reactions, bladder pain, cystitis, bladder spasm, dysuria and hematuria (prescribing information from FDA on Cysview HAL). In addition, the available studies demonstrate improved sensitivity and somewhat reduced specificity for blue light cystoscopy compared with white light cystoscopy; with lower specificity, there is an increased risk of unnecessary biopsy. In the absence of any studies in patients being evaluated for microhematuria, and in light of the known risks, the panel concluded that the risks and burdens of using blue-light cystoscopy in the initial evaluation of patients with microhematuria outweigh the benefits**.** Evidence strength is Grade C because of the poor generalizability to AMH patients, the weak study designs, the heterogeneity of findings, and the small sample sizes.

**Guideline Statement 17.**

**If a patient with a history of persistent asymptomatic microhematuria has two consecutive negative annual urinalyses (one per year for two years from the time of initial evaluation or beyond), then no further urinalyses for the purpose of evaluation of AMH are necessary. *Expert Opinion***

**Discussion.** If the appropriate evaluation of the asymptomatic microhematuria patient does not reveal

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clinically significant urologic or nephrologic disease, then yearly urinalyses should be conducted for at least two years following initial evaluation. If the urinalysis is negative for two consecutive years, then the risk of urologic or nephrologic disease may be no greater than that of the general population. For example, a group of MH positive patients in whom no disease was found after work up (e.g., KUB, ultrasound, cystoscopy, IVU) were followed for four years; the probability of discovering a malignancy during the follow-up period was less than 1% in patients aged younger than 90 years.[215] In addition, a cohort of 234 MH positive male patients aged ≥ 50 years of age at initial testing that underwent a complete evaluation (e.g., cytology, IVU or CT, cystoscopy) and in whom no bladder cancers were detected were followed for 14 years.[118] Two patients eventually developed bladder cancer at 6.7 and 11.4 years after the negative evaluations for a malignancy rate of <1.0%. These data indicate that the overwhelming majority of patients who undergo a thorough initial work up without positive findings will remain cancer-free. Consequently, further urinalyses are unnecessary for work up of the index hematuria episode.

**Guideline Statement 18.**

**For persistent asymptomatic microhematuria after negative urologic workup, yearly urinalyses should be conducted.** ***Recommendation***

**Discussion.** ***(Evidence strength – Grade C; Benefits outweigh risks/burdens).*** The benefits of annual urinalyses in patients with a negative initial evaluation include early diagnosis of a developing, non-visualized urologic disorder. The risks/burdens of urinalyses are minimal. The Panel reviewed 26 studies reporting outcomes for 29,063 patients of which 27,624 had data on follow up. This body of evidence is Grade C because there are significant confounding variables within each of these studies including differing initial workup protocols, unclear follow-up intervals, and unclear follow-up workup protocols. However, they do offer some limited conclusions to guide clinical care. This body of evidence appears to indicate that although the majority of pathologic conditions are captured on a thorough initial workup, a small proportion of AMH patients have disease states that are not initially detected but that progress over time and are identified on later evaluations.[41, 48] Also, since the incidence of urologic lesions increases with age, it is logical to assume that follow-up in an at-risk population may help in early detection leading to treatment of potentially life -threatening lesions.

In addition to malignant findings, patients who undergo an initial negative evaluation for AMH may also be at risk for other non-malignant disease processes.[51] These include urolithiasis, obstructive uropathy such as strictures, infectious processes such as tuberculosis, and medical renal disease such as glomerular nephropathy. A small percentage of AMH patients ultimately will be diagnosed with a nephrologic condition requiring intervention and may present later with dysmorphic red blood cells (RBCs) detected by conventional microscopy, phase-contrast microscopy, or automated analysis.[85-114] These patients may benefit by subsequent referral to a nephrologist, particularly if the hematuria is accompanied by hypertension, proteinuria or other evidence of glomerular disease.

Patients most in need of yearly testing are those in the higher risk population for development of subsequent disease. These include; age greater than 35 years, those with current or past tobacco use, history of pelvic irradiation, cyclophosphamide or other carcinogenic alkylating agent exposure, and exposure to occupational hazards such as dyes, benzenes, and aromatic amines. Follow up of these high-risk patients is even more important because microhematuria may precede the diagnosis of bladder cancer by many years.[10-13, 62]

**Guideline Statement 19.**

**For persistent or recurrent asymptomatic microhematuria after initial negative urologic work-up, repeat evaluation within three to five years should be considered.** ***Expert Opinion***

**Discussion.** No pathological source of MH is found in some 37.3% to 80.6% of patients referred for evaluation of AMH.[30, 35, 41, 48, 50-52, 64, 76, 128] The proportion with no definitive etiology of MH may be even higher among patients found to have AMH in screening populations.[17, 22, 27, 39, 74, 216] Thus, the management of patients with a history of AMH and a prior negative workup is a common clinical scenario and warrants some attention.

While the Panel did identify several cohort studies[17, 22, 41, 51, 64] that reported the outcomes of AMH patients followed after a negative work up, these publications did not include sufficient detail about or comparisons between different follow-up protocols (e.g., between frequency of re-testing, triggers for further workup, and duration of surveillance) to draw conclusions about the optimal strategy. As one might expect, the likelihood of finding significant urologic diagnoses on subsequent workup, particularly urologic cancers, appears to be related to the risk factors within the population being studied. More cancers were found in studies of patients referred for initial (DL) workup of MH (as opposed to those detected by screening), populations of older patients, and populations with a higher proportion of

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male patients. Fewer cancers were found in follow-up studies where patients underwent a complete MH evaluation at baseline, or those where follow-up information was ascertained by chart review, rather than by subsequent testing at intervals. For example, Jaffe[51] studied 372 patients with AMH (median age 58 years) who had a negative cytology, cystoscopy and renal ultrasound at baseline. The authors followed a subset of 75 patients who underwent IVU for persistent AMH on subsequent urinalysis and found two ureteral and one renal cancer in this cohort (4%). A comparably aged female population had no malignancies found after prolonged follow up (though IVU was performed at baseline).[30]

Based on the findings of these studies and recognizing the limitations of our diagnostic techniques, the Panel's Expert Opinion is for follow-up urinalysis after a negative workup, at least once every year for at least two years (see Guideline Statement 19). If the urinalysis is negative at each follow-up, the patient may be released from care, with instructions to return if new symptoms develop or subsequent urine studies show the presence of MH. The clinician may re-evaluate patients whose urine is recurrently positive for MH within three to five years of the initial negative workup. Changes in the clinical scenario, such as a substantial increase in the degree of MH, the detection of dysmorphic RBCs with concomitant hypertension and/or proteinuria, the development of gross hematuria, pain, or other new symptoms, may warrant earlier re-evaluation and/or referral to other practitioners such as nephrologists. The threshold for re-evaluation should take into account patient risk factors for urologic pathologic conditions such as malignancy as well as the fact that patients who had had a thorough initial workup with negative findings are likely to remain cancer-free[118] (see Discussion under Guideline Statement 19).

Patients with causes of AMH that persist and may not require intervention, such as those with enlarged prostate and friable surface vessels, or those with Randall's plaques and non-obstructing stones, present a special challenge since malignant causes of AMH may be masked by the presence of these other entities. The Panel suggests that these patients undergo surveillance urinalysis as above for patients with a negative initial AMH evaluation, and that clinicians use judgment and knowledge of risk factors to decide when and whether to perform a re-evaluation.

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**Research Needs and Future Directions**

Asymptomatic microhematuria is a sign, not a diagnosis or health condition. As a result, existing research on the topic is more limited than that available in many topics covered by AUA Guidelines. Nevertheless, this is one of the most common clinical scenarios physicians face, and based on the existence of widespread screening in the absence of evidence to support its role,[217] there is significant room to improve understanding of this scenario and its management.

**Table 3. Information To Be Reported in Future AMH Studies**

| | |
|---|---|
| **Patient Information** | Detailed patient inclusion/ exclusion criteria |
| | Detailed patient demographics, including age, gender, race/ ethnicity, occupation, and smoking status |
| | Patient past medical and surgical history relevant to conditions associated with AMH, including renal or urological disease, trauma or instrumentation, anticoagulation medication use |
| **AMH Diagnosis Methods & Findings** | Initial diagnosis methods (e.g., dipstick, microscopy) and findings |
| | Whether dipstick or microscopy was repeated prior to diagnostic workup |
| | Type of dipstick, use of automation, methods for and findings of microscopic examination, including results of urine specific gravity and protein |
| **Workup Methods & Findings** | Description of all workup methods, including laboratory tests, cytology, urine markers, cystoscopy, and imaging |
| | Findings from all workup methods |
| | Report of findings for patients overall as well as for clinically important subgroups (i.e., males, smokers, older patients, patients with other risk factors) |
| **Follow-Up Methods & Findings** | Description of follow-up protocols in AMH patients with negative findings on initial workup, including periodicity of repeat urinalyses |
| | Description of repeat evaluation methods and trigger for repeat evaluation |
| | Findings from repeat evaluation |

Furthermore, the panel recognizes that although randomized controlled trials are the gold standard for obtaining evidence to structure care, it is not likely that these will occur broadly on this specific topic based on limited finances and resources to consider related questions when other pressing and more compelling clinical issues are likely to attract these resources. Thus, high quality reporting of single institution or collaborative experiences or registry studies may be the hallmark of future reports. If that is the case, it is imperative that authors publish robust information regarding baseline characteristics of the populations reported, evaluation strategies utilized, and long term surveillance protocols in place (See Table 3). The ability to stratify evaluation strategies based on the probability of an underlying serious condition for patients with specific characteristics is currently compromised by the lack of this type of basic information.

**Etiology.** Disease-related causes of AMH are well described, but there is little understanding of the underlying cause in patients with an initial negative evaluation. Identification of a marker or other method to define a benign cause could lead to improved risk stratification, especially in the patient with persistent AMH following an initial evaluation.

**Evaluation Techniques.** A growing body of work exists regarding the risk of imaging and contrast agents necessary for characterization of patients with AMH. The panel determined that the benefit of identifying significant pathology outweighs the risk of the evaluation. Nevertheless, there is significant need for even safer contrast agents, or preferably to identify accurate imaging techniques that would not require contrast agents. Recognizing this may be difficult, it is still appealing to identify even a screening evaluation technique that would potentially allow low risk patients to forego contrast agents (i.e. ultrasound). This would ideally also avoid or decrease the dose of ionizing radiation. In lieu of such innovations, there is need for identification of strategies or agents that can limit the risk of contrast agents from both a toxicity and allergic reaction standpoint.

With the potential that it might allow avoidance of ionizing radiation and avoids traditional contrast agents, MRU is recommended as an alternative to multi -phasic CT for patients at risk. Nevertheless, the role of MRU in this specific patient population is not well defined in the published literature, and merits further evaluation.

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The risk of cystoscopy is very low, so it is unlikely that any alternative would be identified that would improve upon this technique. Nevertheless, further efforts at improving patient experience regarding discomfort of the examination are worthwhile. Innovative imaging techniques such as blue light cystoscopy, narrow band imaging, or virtual cystoscopy will require substantial research before it is likely that they will become part of the evaluation, and this should include analysis of costs if they are to play a role in the future healthcare environment.

The panel feels that emphasis of research for such diagnostic techniques should approach the question with clarity regarding the need for sensitivity compared to specificity. For example, cystoscopy has proven to be exceedingly sensitive in this specific clinical setting (this is not as clearly established in the bladder cancer patient population, probably based on the difference in prevalence of small, difficult to visualize bladder cancers in the underlying populations). The sensitivity is shown to be high regarding AMH evaluation based on the rarity of identification of bladder cancer following an initial negative evaluation. Thus, it would be unlikely to find value of new techniques such as narrow band imaging and blue light cystoscopy in the evaluation of AMH if their appeal is based on being more sensitive than cystoscopy. Nevertheless, it is possible that emerging technologies may be able to improve upon the specificity of cystoscopy in order to avoid unnecessary biopsies or further investigations.

Infectious risk of cystoscopy is low, and the Best Practice Policy Statement on Urologic Surgery Antimicrobial Prophylaxis (2008)[117] specifically recommends against routine use of antibiotics for routine cystoscopy. With the recognition that antibiotic resistance is rapidly increasing, the potential for overuse of antibiotics in urological practices to be a contributing factor in subsequent multidrug resistance merits further investigation.

**Natural history.** The panel recognizes that there is almost no published information to guide the decision regarding follow-up after a negative evaluation for AMH. It is recognized that it is uncommon for patients to present in the future with significant findings that appear to have been missed by initial evaluation, but medical, socioeconomic, anxiety, and legal implications create need for this scenario to be further considered.

**Economic considerations.** With the high prevalence of AMH in the population in an era of increasing resource constraints, it would be naïve to ignore economic considerations in future investigations. Most patients who present with this condition have no underlying significant abnormality, so limiting financial expenditures on evaluations of those individuals is particularly appealing. Nevertheless, it is imperative not to allow this to lead to inadequate investigation in the patients who have serious underlying causes, so efforts towards improved risk stratification or triage strategies that allow some patients with AMH to avoid full investigation merit careful consideration. This might involve investigation of urine or serum based tests that could have a high enough sensitivity that a negative test might avert unnecessary invasive and radiological evaluation. Currently, the available literature does not allow evidence-based risk stratification.

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**CONFLICT OF INTEREST DISCLOSURES**

All panel members completed COI disclosures. Relationships that have expired (more than one year old) since the panel's initial meeting, are listed. Those marked with (C) indicate that compensation was received; relationships designated by (U) indicate no compensation was received.

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This document was written by the Asymptomatic Microhematuria Guidelines Panel of the American Urological Association Education and Research, Inc., which was created in 2009. The Practice Guidelines Committee (PGC) of the AUA selected the panel chair. Panel members were selected by the chair. Membership of the panel included urologists and other clinicians with specific expertise on this disorder. The mission of the committee was to develop recommendations that are analysis-based or consensus-based, depending on Panel processes and available data, for optimal clinical practices in the diagnosis and treatment of asymptomatic microhematuria.

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While these guidelines do not necessarily establish the standard of care, AUA seeks to recommend and to encourage compliance by practitioners with current best practices related to the condition being treated. As medical knowledge expands and technology advances, the guidelines will change. Today, these evidence-based guideline statements represent not absolute mandates but provisional proposals for treatment under the specific conditions described in each document. For all these reasons, the guidelines do not pre-empt physician judgment in individual cases.

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