Quality and cost assessment of Canadian Urological Association microscopic hematuria guidelines in clinical practice: Turning urine into gold

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Mark A. Assmus, MD[1]; David B. Beyer, MD[2]; Joan Hanks, MD[3]; Mathew Estey, MD[2,3]; Keith F. Rourke, MD[1]; Trevor Schuler, MD[1]; Tim A. Wollin, MD[1]

[1]Department of Surgery, Division of Urology, Edmonton, AB, Canada; [2]Department of Laboratory Medicine and Pathology, Edmonton, AB, Canada; [3]DynaLIFE Medical Laboratories, Edmonton, AB, Canada

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Abstract

Introduction: Asymptomatic microscopic hematuria (AMH) is defined in the Canadian Urological Association (CUA) guideline as >2 red blood cells (RBCs) per high-powered field (HPF). Our objective was to evaluate guideline adherence for AMH at our center. Secondarily, we aimed to identify areas of the guideline that can be optimized.

Methods: We retrospectively reviewed 875 consecutive adults referred to two urologists for hematuria between June 2010 and June 2016. Patient characteristics, risk factors, and outcomes were added to an encrypted Research Electronic Data Capture (REDCap) database. Evaluation of microscopic hematuria reporting was performed by analyzing 681 urine samples reported as 1–5 RBC/HPF. Healthcare costs were obtained from Alberta Health Services (AHS), Data Integration and Management Repository (DIMR), and Alberta Society of Radiologists (ASR).

Results: Of the 875 patients referred with hematuria, 400 had AMH. Overall, 96.5% completed evaluation consistent with the CUA guideline. The incidence of pathology requiring surgical intervention was 21/400 (5%) with a 0.8% rate (3/400) of urothelial cell carcinoma (UCC) (non-invasive, low-grade). No malignancy was found in non-smokers with normal cytology, normal imaging and <50 RBC/HPF; 44% had AMH in the 1–5 RBCs/HPF range. Only 41% (279/681) of urine samples categorized as 1–5 RBCs/HPF had guideline-defined microscopic hematuria. By changing local microscopic hematuria reporting to differentiate 1–2 and 3–5 RBCs/HPF, we estimate $745 000 in annual savings.

Conclusions: At our center, CUA AMH guideline adherence is high. We did not find malignancy in non-smokers with normal cytology, imaging and <50 RBC/HPF. We identified and changed regional microscopic hematuria reporting to fit the CUA definition, eliminating unnecessary investigations and healthcare costs.

Introduction

Microscopic hematuria (MH) is a common urinalysis abnormality, with a lifetime incidence of 6.5% in the general population.[1-5] Although there are potential benign causes, ruling out genitourinary (GU) malignancies as the etiology for asymptomatic microscopic hematuria (AMH) is paramount. In reviewing the literature, MH is associated with a 0.5–10.5% rate of bladder cancer.[1-5] Despite the importance of evaluating the correct patients in a comprehensive manner, there remains a lack of consensus among international guidelines, as exemplified by contrasting the American Urological Association (AUA), Canadian Urological Association (CUA), and European guidelines for investigating hematuria.

In examining our most recent 2009 CUA guideline (Note: this guideline is currently being updated), MH is defined as >2 red blood cells (RBCs) per high-powered field (HPF) on two microscopic urinalysis (UA) without recent exercise, menses, sexual activity, or instrumentation.[6] Subsequent evaluation consists of a history, physical exam, urine cytology, and upper tract imaging in the form of an ultrasound (US) or computed tomography (CT) with urogram phase. Cystoscopy is performed on patients >40 years old or with a positive/atypical urine cytology.[6] In patients ≤40 years old, only those with risk factors for urothelial malignancy should proceed to cystoscopy.[6] Risk factors include smoking history, occupational chemical exposure, pelvic radiation, cyclophosphamide, and storage symptoms.

In contrast, the 2008 British guideline approach hematuria by defining visible or non-visible hematuria on a voided dipstick.[7] Cystoscopy evaluation is required for patients ≥40 years old.

In 2016, Bladder Cancer Canada (BCC), the Canadian Urologic Oncology Group (CUOG), and CUA published a consensus recommendation to improve bladder cancer care in Canada.[8] They reviewed the CUA MH guideline with the following recommendations: urine cytology reserved

for gross hematuria (GH) or symptomatic hematuria; follow negative workup patients annually with UA and cytology for three years (if two consecutive normal UA, then discontinue further workup); if MH persists or degree worsens, consider repeat evaluation every 3–5 years.[8] Also, similar to the 2012 AUA guideline update, the authors recommend decreasing the age cutoff for patients requiring cystoscopy evaluation to ≥35 years old irrespective of risk factors.[8,9]

Of particular interest to our center, and despite a paucity of evidence, guidelines that use urine microscopy in the definition of AMH unanimously use a cutoff of >2 RBC/HPF to represent microscopic blood in the urine. At the initiation of this study, the Edmonton Zone reported urine hematuria microscopy ranges of: 0, 1–5, 6–10, 11–25, 26–50 or >50 RBCs/HPF. Due to these long-standing reporting practices, remotely established Edmonton Zone Urology Referral Reference (EZURR) guideline recommended that primary care physicians (PCPs) refer patients with >5 RBCs/HPF for MH evaluation. This difference in EZURR and CUA recommendations resulted in variable referring of patterns, with some PCP clinics referring all patients with 1–5 RBCs/HPF and other clinics only referring those with >5 RBCs/HPF.

From the perspective of efficient and effective healthcare resource utilization, determining which patients need cystoscopic evaluation of the lower urinary tract (LUT) for MH is crucial. At our centralized ambulatory Northern Alberta Urology Center (NAUC), approximately 2400 screening cystoscopies are performed annually for AMH, representing a substantial use of resources. Additionally, cystoscopy is an invasive investigation that is associated with significant patient anxiety.[10-12] Working within the Canadian universal healthcare model, a push for practice pattern changes, such as the Choosing Wisely campaign, prompted us to ensure our current guideline investigations are detecting significant pathology (those requiring medical or surgical intervention or of importance to patients) in an efficient manner.[13,14]

The objective of this study was to examine our local practice for a cohort of adult patients referred for evaluation of MH and to identify the incidence of clinically significant pathology. We hoped to examine guideline adherence and ensure we were providing patients with correct investigations, and to highlight potential quality improvement targets to minimize incomplete workups, loss to followup, or unnecessary healthcare expenses.

Methods

Study design

After receiving institutional review board approval, we retrospectively reviewed 875 consecutive adults that were seen in urological consultation for hematuria in Edmonton, AB, Canada by two urologists (KFR and TAW) between June 2010 and June 2016. Of these 875 patients with hematuria, 400 had been referred for evaluation of AMH. Patient characteristics, hematuria history, UCC risk factors, investigations, and outcomes were collected and managed using an encrypted Research Electronic Data Capture (REDCap) tool hosted at the University of Alberta.

Outcome measures

For our primary outcomes, we assessed detection of urothelial malignancy and adherence to guideline recommendations. Clinically significant urological diagnoses included both malignant and non-malignant diagnoses that may require medical or surgical intervention or could be important to patients. We systematically reviewed all aspects of each patients AMH workup (history, physical, upper tract imaging, lower tract imaging, cystoscopy evaluation) and recorded the frequency of all malignant and non-malignant abnormalities detected (malignant tumors, benign cysts, benign tumors, congenital/anatomic abnormalities, urinary tract calculi, adrenal abnormalities, bladder outlet obstruction [BOO]). Additionally, non-urological incidentally detected abnormalities were recorded (peripheral vascular disease/aneurysms, uterine fibroids, ovarian cysts, bowel abnormalities). Secondary quality assessment (QA) outcomes involved analyzing 681 urine samples reported to have 1–5 RBCs/HPF that underwent microscopy evaluation on three regional DynaLIFE Medical Labs analyzers over two consecutive days in the Edmonton Zone. Within the reporting category of 1–5 RBs/HPF, we identified the proportion of samples that had clinically significant hematuria (>2 RBCs/HPF). Regional healthcare costs for the minimal CUA guideline recommended workup of AMH were obtained from Alberta Health Services (AHS), Alberta Medical Association (AMA), Data Integration and Management Repository (DIMR), and Alberta Society of Radiologists (ASR). We specified one confirmatory urinalysis, urine cytology, upper tract imaging via US of the kidneys, ureter and bladder, as well as urological consultation with lower tract evaluation via cystoscopy in order to estimate the per-patient cost of the minimal workup for AMH at our center.

Statistical analysis

Continuous variables are expressed as mean, median, and range while proportions were used for categorical variables. GraphPad Prism (v6.0 Inc., La Jolla, California, U.S.) was used for our statistical analysis, including one-way ANOVA analysis with Tukey's multiple comparisons test set to a significance of 0.05 (95% confidence interval [CI]).

Results

Patient characteristics

A total of 875 consecutive hematuria referrals seen by two urologists in Edmonton, Alberta from June 2010 to June 2016 were reviewed; 400/875 (46%) had AMH and 70 patients were excluded because they either did not have microscopic or gross hematuria warranting a referral (n=31) or they did not have reviewable data (n=39). The remaining patients were referred for gross hematuria and not included.

Table 1 outlines patient characteristics of the 400 MH referrals; 262/400 (66%) patients were female with an overall mean age at consultation of 59 years (range 19–102). There was no mean age difference at consultation between male (60 years old) and female (58 years old) patients ($p>0.05$). Overall, 33/400 (8%) of patients were ≤40 years old, with no difference between gender (15 vs. 18 male:female patients, $p>0.05$).

The mean and median times from first positive UA to consultation were 34 and 11 months, respectively. There was no difference in median time to consultation between male and female patients (11 vs. 12 months, respectively; $p>0.05$).

Urothelial cell carcinoma (UCC) risk factors

One hundred forty of 400 (35%) patients identified smoking at least one pack year within the 10 years leading up to their consultation; 82 (59%) of these patients actively smoked at the time of consultation. Six of 400 (2%) had additional UCC risk factors, including pelvic radiation (2), heavy petroleum exposure (2), cyclophosphamide (1), and dye/textile industry (1).

Urine dipstick/UA

Five percent of patients did not have hematuria detected on a reviewable urine dipstick prior to referral (including no dipstick performed, 0 RBCs/HPF, trace hematuria/referring physician reported hematuria). The highest proportion of referrals had a maximum of 1+ hemoglobin on urine dipstick (45%), followed by 34% with 2+, and 14% with 3+ hemoglobin. Of note, 2% of patients were referred for MH with 4+ hemoglobin levels.

The largest proportion (44%) of patients referred for evaluation had 1–5 RBCs/HPF as the highest observed degree of MH. The remaining breakdown of MH findings revealed 6–10 (19%), 11–25 (21%), 26–50 (6%), and >50RBCs/HPF (10%).

Table 1. Characteristics for patients that underwent MH workup by two urologists in Edmonton, AB between June 2010 and 2016

Characteristic	Male	Female	Total
Patients, n (%)	138 (34)	262 (66)	400 (100)
Mean age at consult, years (range)	60 (19–102)	58 (24–91)	59 (19–102)
≤40 years old, n (%)	15 (11)	18 (7)	33 (8)
>40 years old, n (%)	123 (89)	244 (93)	367 (92)
Average time (months) from +UA to consult (mean/median)	30/11	37/12	34/11
Range time (months) from +UA to consult	1–168	1–300	1–300

UA: urinalysis.

Urine cytology

Of the 400 patients, 350 (88%) had benign cytology, 32 (8%) atypical, 18 (4%) were not recorded, and none (0%) were malignant. Of the 32 atypical urine cytology patients, imaging revealed two patients with benign renal cysts on US, four patients with non-obstructing renal calculi, one patient with a moderately elevated post-void residual secondary to benign prostatic hyperplasia (BPH), and one patient with an atrophic left renal moiety. Cystoscopy evaluation of these 32 patients with atypical urine cytology revealed two patients with bladder tumors, three patients with cystitis cystica, one patient with a bladder calculus, one patient with a urethral stricture, and two patients with friable and trabeculated bladder walls. Final pathology on the two bladder tumors revealed one patient with low-grade superficial (Ta) UCC and the other with non-malignant inflammatory changes.

Genitourinary tract imaging

A total of 333/400 (83%) patients underwent appropriate imaging prior to consultation; 85% revealed benign imaging, with the 15% of detected upper tract and lower tract abnormalities, outlined in Figs. 1 and 2.

Cystoscopy

Most (383/400, 96%) patients underwent cystoscopy. Of the 17 patients who did not undergo cystoscopic workup, six did not meet CUA guideline recommendations for requiring a cystoscopy, two had no data recorded, five were no-shows, and four patients refused the procedure.

In 328/383 (86%), cystoscopies were normal. Five of the 383 (1%) revealed a bladder tumor, and 50/383 (13%) had incidental non-malignant abnormalities identified, including the following etiologies potentially requiring surgery: bladder tumor, urethral stricture, bladder calculi, and severe BPH. Three of five of the bladder tumors were positive for malignancy on final pathology.

Bladder tumor detection

Five bladder tumors were identified. One of these tumors was detected on pre-cystoscopy imaging in the form of unilateral hydronephrosis (final pathology low-grade superficial UCC), with the remaining four having normal upper tract

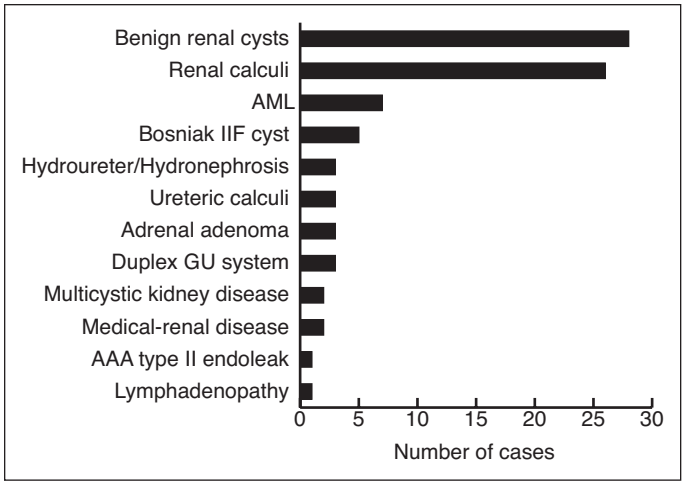

Fig. 1. Frequency of abnormalities detected on upper tract imaging for microscopic hematuria evaluation. AAA: abdominal aortic aneurysm; AML: angiomyolipoma; GU: genitourinary.

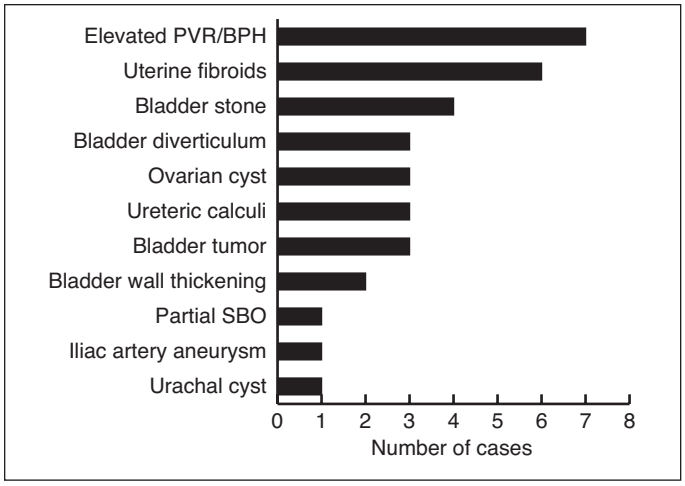

Fig. 2. Frequency of abnormalities detected on lower tract imaging for imaging for microscopic hematuria evaluation. BPH: benign prostatic hyperplasia; PVR: post-void residual; SBO: small bowel obstruction.

imaging. Three (60%) were malignant, low-grade superficial UCC, with the remaining two patients having non-malignant inflammatory findings. Table 2 breaks down the characteristics of the five patients with bladder tumors. Overall, comprehensive evaluation for AMH revealed 21/400 (5%) patients requiring surgical intervention; of these 21 patients, five underwent surgical intervention for bladder masses, eight for BOO/BPH/urethral stricture, four for bladder calculi, three for ureteric calculi, and one for urachal mass/cyst.

Guideline adherence

Twenty-one of 400 (5%) MH workups identified significant pathology requiring further surgical intervention; 14 (3.5%) patients were ≤40 years old with normal upper tracts, urine cytology, no UCC risk factors, and AMH. Deviating from the guidelines, 8/14 of these patients underwent cystoscopy, revealing one patient with cystitis cystica.

Urine microscopy reporting

Forty-one percent (279/681) of urine samples categorized as having 1–5 RBCs/HPF had guideline-defined MH (>2 RBCs/HPF) on final review.

Cost savings

With 44% of MH referrals having 1–5 RBCs/HPF and 41% of these patients having guideline-defined MH (>2 RBCs/HPF), we can estimate that 103/400 patients underwent unnecessary MH comprehensive investigations and surgical consultation. Extrapolating these results to all patients referred to the Northern Alberta Urology Centre (NAUC) seen by one of 15 adult staff urologists for MH, roughly 620 patients are being referred and investigated unnecessarily on an annual basis. Using costing data outlined in Table 3, the conservative regional cost of evaluating AMH is $1196.85/patient. By changing the Edmonton Zone microscopic hematuria reporting into separate categories for 1–2 RBCs/HPF and 3–5 RBCs/HPF, we estimate $745 000 in annual healthcare savings, as seen in Fig. 3.

Discussion

Overall, <1% (3/400) of patients referred to our center for MH workup had a malignancy diagnosed. Although this falls within the range reported in the literature (0.5–10.5%),[1-5] by interrogating our regional MH laboratory reporting ranges, we detected that approximately 25% of patients that were evaluated did not have MH per the CUA definition.

Table 2. Characteristics of patients with bladder tumors detected on MH evaluation

Age/Sex	Max UA (RBCs/hpf)	AMH duration (months)	Smoker (Y/N)	Cytology	Imaging	Cysto results	Pathology
66/F	1-5	5	N	Benign	Unilateral hydro	Left UO and dome polyp	LG-Ta UCC
58/F	>50	6	N	Benign	Normal	Polyp	LG-Ta UCC
67/F	26–50	90	N	Atypical	Normal	Right UO mucosal lesion	Non-malignant
77/M	11–25	142	Y	Unknown	Normal	Polyp	LG-Ta UCC
51/F	11–25	4	Y	Benign	Normal	Inflammatory/ edematous patches	Non-malignant

F: female; LG: low-grade; M: male; UA: urinalysis; UCC: urothelial cell carcinoma; UO: ureteric orifice.

Table 3. Local cost of base investigations recommended by CUA guidelines for AMH

Investigation	Cost ($)
Urinalysis + microscopy	7.03
Urine cytology	32.82
Surgical specialist clinical consultation (Comprehensive AHS clinic facility costs)	359.00
Upper tract imaging evaluation (radiologist & ultrasound – kidney, ureter, bladder)	173.00
Lower tract procedural evaluation (cystoscopy)	447.00
Urologist	178.00
AMH consultation	-93.00
Cystoscopy performed	-85.00
Total	**1196.85**

AHS: Alberta Health Services; AMH: asymptomatic microscopic hematuria; CUA: Canadian Urological Association.

Despite our low rate of detecting cancer, referral to a urologist with comprehensive evaluation of the upper and lower tracts did detect multiple non-malignant findings that required further management. With 5% of referred patients having an abnormality that warrants surgical intervention and a large proportion initiating medical management, the value of investigating this cohort was reinforced.

As noted above, when reviewing our preliminary data, we identified that within the regional laboratory services in Edmonton, urine microscopy was not reported in a range that allowed identification of patients requiring MH workups per the CUA guideline. Abnormal urine microscopy was reported if there was anywhere from 1–5 RBCs/HPF, including patients with ≤2 RBCs/HPF. Once we identified that this potentially leads to a proportion of MH referrals for patients who only have 1–2 RBCs/HPF and do not truly have MH, we collaborated with DynaLIFE Medical Labs and the Department of Laboratory Medicine and Pathology to perform a of UA reporting. This QA ultimately confirmed that a large proportion of UA reporting 1–5 RBCs/HPF were not detecting guideline-defined MH. Using this data, we initiated a region-wide change in urine microscopy reporting so that 1–2 RBCs/HPF and 3–5 RBCs/HPF were reported separately as of June 1, 2018.

By reporting the proportion of patients with guideline-defined MH (>2 RBCs/HPF) in the 1–5 RBCs/HPF category, we will prevent approximately 620 unnecessary comprehensive investigations for MH in our region per year. Including upper tract imaging, urine cytology, cystoscopy, and specialist consultations (estimated $1196.85/patient), this could translate into $745 000 saved annually. This is a conservative estimate of savings since many patients will ultimately undergo many urine tests (UA, urine cytology) along with additional imaging (CT urogram) as part of their AMH workup. We acknowledge that we are reporting savings from a healthcare payer perspective and did not take into account time off work and loss of potential earnings.

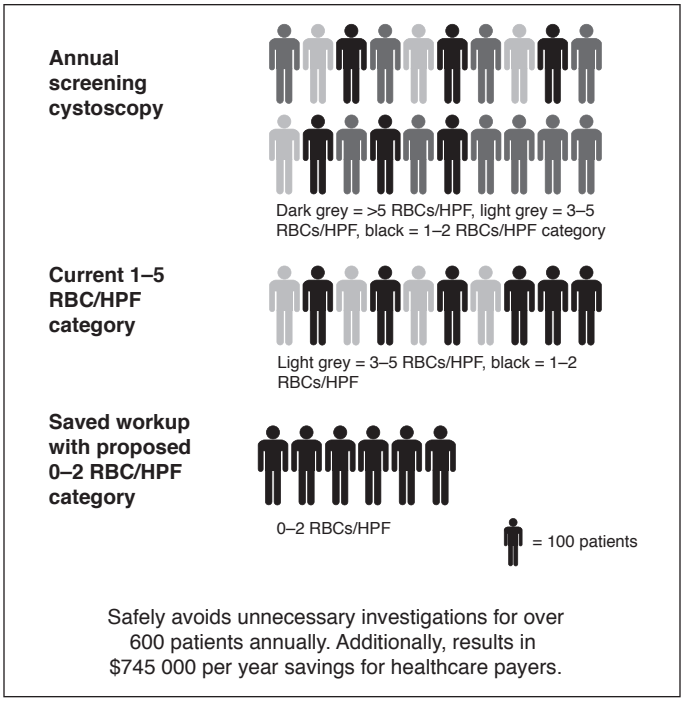

Fig. 3. Predicted patient care and healthcare resource benefit of implementing differentiated reporting ranges for microscopic hematuria in the Edmonton zone (0–2 RBCs/HPFand 3–5 RBCs/HPF).

Importantly, aside from cost savings, we can prevent numerous invasive procedures and psychological stress associated with a potentially unnecessary workup for MH in these patients. Alternatively, PCPs that previously followed EZURR referral guideline (referral trigger of >5 RBC/HPF) now have the ability to correctly identify and refer patients with 3–5 RBC/HPF. This will lead to an increase in appropriate comprehensive investigations for MH.

One ongoing topic of discussion among the various MH guidelines is the age cutoff for patients requiring lower tract cystoscopy (40 vs. 35 years old). In our study, very few patients ≤40 years old were referred for MH evaluation (33 patients). Similar to a recent publication by Lippmann et al, the patients who had UCC detected in our cohort were older (>55 years old) and had a history of smoking or abnormal imaging.[15] From the perspective of the recently published Canadian bladder cancer consensus paper, broadening the age range for who should proceed to cystoscopy only adds a small additional population/resource utilization pressure on the system, while ensuring that most bladder tumors are detected. If we examine our patients that fall within this debated age range, only 14 patients were ≤40 years old with normal upper tracts, urine cytology, no UCC risk factors, and AMH that did not have another indication for cystoscopy. Eight of these patients proceeded to cystoscopy without the detection of any pathology. Per the current CUA guideline, these patients were subject to potentially unnecessary investigations and used additional healthcare resource-

Surprisingly, we noted a longer time from first positive MH UA to urology consultation than anticipated (>12 months). One major reason for this timeline was the time between serial UAs and duration required to complete upper tract imaging. This may be, in part, due to the high-volume nature of the NAUC, with its associated large catchment area. Many patients referred for urological evaluation come from small northern Canada communities with barriers that may lead to delayed access to care (e.g., CT imaging). We expect this time to urological consultation and cystoscopy evaluation to improve with our corrected UA MH reporting cutoffs, which may decrease the annual MH referrals triaged at our center.

With respect to the urine cytology and cystoscopy results, only 32 patients had atypical cytology, with one having an ultimate diagnosis of a low-grade UCC. This relatively inexpensive and easy-to-collect investigation may continue to have a screening/surveillance role for this patient population. Only 2.75% of patients referred for MH did not receive a cystoscopy when it was indicated, reinforcing excellent CUA guideline adherence.

Study limitations included the retrospective nature of our review. Details on patient smoking history, risk factors, and investigations prior to consultation were variable. Also, some patients seen at our center live >300 km away and may have laboratory investigations from neighboring provinces (British Columbia, Saskatchewan) that are not reviewable. Additionally, we did not attempt to perform a comprehensive cost-benefit analysis for MH workup at our center, as the true global costs to the healthcare system extends beyond just the costs of each individual test and was not the intent of the study. In this study, we performed a QA of MH evaluation at our center and identified a cohort of patients that did not have clinically significant MH. For these patients, we determined the approximate investigative health are costs that were used in their evaluation.

Taken together, the results of this study have significant implications with respect to specialist responsibility to audit and perform ongoing QA assessments to ensure appropriate care and healthcare resources utilization. We identified that a simple and quick change in urine microscopy reporting within our region could result in fewer unnecessary investigations, cost savings, and potential wait time improvements for patients that have indications for cystoscopy.

Conclusions

At our center, adherence to CUA MH guideline appropriately evaluates patients who require further intervention. We did not find any malignancy in non-smokers with normal cytology, normal imaging, and <50 RBCs/HPF. By interrogating local practices, we identified and subsequently implemented a change in local MH reporting. The new Edmonton Zone MH reporting cutoffs will significantly reduce unnecessary patient investigations and healthcare costs.

Competing interests: Dr. Rourke has been an advisory board member for and is a shareholder of Boston Scientific; he is also a study investigator for Red Leaf Medical. The remaining authors report no competing personal or financial interests related to this work.

This paper has been peer-reviewed.

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Correspondence: Dr. Tim A Wollin, Department of Surgery, Division of Urology, Edmonton, AB, Canada; twollin@ualberta.ca

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