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Cost-effectiveness of Common Diagnostic Approaches for Evaluation of Asymptomatic Microscopic Hematuria

Joshua A. Halpern, MD, MS; Bilal Chughtai, MD; Hassan Ghomrawi, PhD, MPH

IMPORTANCE Asymptomatic microscopic hematuria (AMH) is highly prevalent and may signal occult genitourinary (GU) malignant abnormality. Common diagnostic approaches differ in their costs and effectiveness in detecting cancer. Given the low prevalence of GU malignant abnormality among patients with AMH, it is important to quantify the cost implications of detecting cancer for each approach.

OBJECTIVE To estimate the effectiveness, costs, and incremental cost per cancer detected (ICCD) for 4 common diagnostic approaches evaluating AMH.

DESIGN, SETTING, AND PARTICIPANTS A decision-analytic model-based cost-effectiveness analysis using inputs from the medical literature. PubMed searches were performed to identify relevant literature for all key model inputs, each of which was derived from the clinical study with the most robust data and greatest applicability. Analysis included adult patients with AMH on routine urinalysis with subgroups of high-risk patients (males, smokers, age ≥50 years) seen in the primary care or urologic referral setting.

INTERVENTIONS Four diagnostic approaches were evaluated relative to the reference case of no evaluation: (1) computed tomography (CT) alone; (2) cystoscopy alone; (3) CT and cystoscopy combined; and (4) renal ultrasound and cystoscopy combined.

MAIN OUTCOMES AND MEASURES At termination of the diagnostic period, cancers detected, costs (payer perspective), and ICCD per 10 000 patients evaluated for AMH.

RESULTS Of the 4 diagnostic approaches analyzed, CT alone was dominated by all other strategies, detecting 221 cancers at a cost of $9 300 000. Ultrasound and cystoscopy detected 245 cancers and was most cost-effective with an ICCD of $53 810. Replacing ultrasound with CT detected just 1 additional cancer at an ICCD of $6 480 484. Ultrasound and cystoscopy remained the most cost-effective approach in subgroup analysis. The model was not sensitive to any inputs within the proposed ranges. Using probabilistic sensitivity analysis, ultrasound and cystoscopy was the dominant strategy in 100% of simulations.

CONCLUSIONS AND RELEVANCE The combination of renal ultrasound and cystoscopy is the most cost-effective among 4 diagnostic approaches for the initial evaluation of AMH. The use of ultrasound in lieu of CT as the first-line diagnostic strategy will optimize cancer detection and reduce costs associated with evaluation of AMH. Given our findings, we need to critically evaluate the appropriateness of our current clinical practices, and potentially alter our guidelines to reflect the most effective screening strategies for patients with AMH.

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Author Affiliations: Department of Urology, Weill Cornell Medicine, New York, New York (Halpern, Chughtai); Departments of Surgery and Pediatrics, Feinberg School of Medicine, Northwestern University, Chicago, Illinois (Ghomrawi).

Corresponding Author: Joshua A. Halpern, MD, MS, Department of Urology, Weill Cornell Medicine, 525 E 68th St, Starr 900, New York, NY 10065 (jah2031@nyp.org).

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Asymptomatic microscopic hematuria (AMH), the presence of 3 or more red blood cells on urinalysis in the absence of genitourinary (GU) symptoms, is highly prevalent, with population-based studies estimating that up to 40.9% of US adults have this finding on urinalysis.[1,2] Among potential etiologies for AMH, GU malignant abnormality is of particular concern, with studies showing that 0% to 11% of patients with AMH had malignant abnormalities.[3-6]

The high prevalence of AMH and its role as a potential harbinger of malignant abnormality confers great importance on the diagnostic algorithm for its evaluation. Many clinicians and policy makers, including the American Urological Association (AUA), have advocated for diagnostic protocols that maximally detect occult malignant neoplasms, because delays in treatment of GU cancer may result in patient anxiety, impaired quality of life, and poor clinical outcomes.[7,8] Others have sought alternative approaches, predominantly driven by the fact that most evaluations for AMH return negative results for malignant abnormality.[6,9]

The choice of diagnostic protocol for patients with AMH has broad clinical and economic implications. The AUA-recommended protocol, consisting of computed tomographic (CT) urography and cystoscopy, subjects patients to tests that carry considerable risk of morbidity including procedural discomfort, urinary tract infection (UTI), contrast-induced nephropathy (CIN), and radiation exposure, all of which impact quality of life and generate health care costs.[10-15] These costs must be weighed against the relatively low risk of malignant abnormality.[16] Despite the economic burden of AMH evaluation, there have been few studies evaluating its cost-effectiveness, which have either focused on the role of screening urinary biomarkers or predated modern imaging.[17-22] We sought to determine the relative cost per cancer detected among 4 diagnostic protocols for the evaluation of AMH, with particular focus on the radiodiagnostic component, because this is the source of greatest morbidity, cost, and controversy. We hypothesized that the replacement or exclusion of CT from diagnostic protocols would considerably reduce costs with minimal compromise on cancer detection.

Key Points

Question What is the most cost-effective strategy for the initial diagnostic evaluation of patients with asymptomatic microscopic hematuria (AMH)?

Findings In this cost-effectiveness analysis based on inputs from the medical literature, the combination of cystoscopy and renal ultrasound was most cost-effective with an incremental cost of $53 810 per cancer detected.

Meaning The combination of cystoscopy and ultrasound should be considered first-line in the evaluation of patients with AMH.

Methods

Model Overview

We developed a decision-analytic model to simulate cancer detection rates and costs associated with the evaluation of adult patients with AMH. Diagnostic strategies were selected based on international guidelines and alternative approaches endorsed by experts in the literature. Patients entering the model had 3 or more red blood cells on urinalysis, no history of GU malignant abnormality, and concurrent negative urine culture results to exclude UTI. We assumed the presence or absence of GU cancer for each patient on model entry, and this disease status was static throughout. The model horizon was termination of the diagnostic period with either an accurate diagnosis (radiographic or pathologic) or completion of further diagnostic testing for evaluation of false-positive or incidental findings.

Effectiveness was determined by number of cancers detected with each strategy. We used a composite cancer endpoint, which consisted of lower tract (bladder) urothelial, upper tract urothelial (UTUC), and renal cell cancer (RCC). For model purposes, upper and lower tract cancers were considered mutually exclusive. Although these cancers present in tandem, this is an infrequent occurrence owing to the low incidence of UTUC.

The model was programmed in TreeAge Pro (version 2015, TreeAge Software Inc.).

Diagnostic Strategies

Four diagnostic strategies were evaluated. The first strategy, combination of CT and cystoscopy, is considered the gold standard according to AUA guidelines, employing diagnostic tests with the highest accuracy for detection of upper and lower tract cancers, respectively.[23,24] The second strategy, combination of renal ultrasound and cystoscopy, meets the recommendations of multiple international guidelines, including the Dutch Guideline on Hematuria and the guideline of the Canadian Urological Association.[25,26] Furthermore, despite AUA guidelines, many practitioners in the United States use ultrasound in lieu of CT for AMH evaluation.[2] Replacement of CT with ultrasound significantly reduces morbidity through avoidance of radiation and radiographic contrast exposure. Likewise, ultrasound is cheaper and further reduces downstream costs generated by incidental findings on CT, though its sensitivity for cancer detection is inferior.[26,27]

We compared these strategies to cystoscopy alone and CT alone. Cystoscopy alone has been advocated based on the observation that GU tumors associated with AMH are predominantly located in the lower urinary tract, whereas upper tract tumors comprise just 5% of all urothelial neoplasms.[9,28-30] Computed tomographic urography alone has been advocated on the basis of improved sensitivity and specificity of modern CT for detection of lower urinary tract cancers, thereby obviating the need for and sparing the morbidity of cystoscopy.[10,31,32] We did not evaluate ultrasound alone owing to the low sensitivity of ultrasound for detection of lower tract malignant abnormalities, which accounts for the majority of GU malignant abnormalities in patients with AMH, thereby rendering ultrasound alone a poor strategy for initial detection of malignant abnormalities in this population.[33,34]

We did not incorporate voided urine cytology into the above diagnostic strategies because the AUA recommends

Table 1. Base Case Inputs and Ranges Used in Sensitivity Analysis

Variable	Incidence Rates (Range)	References
Cancer Incidence		
Lower tract	0.023 (0.000-0.081)	Loo et al, 2013[2]; Golin et al, 1980[6]; Messing et al, 2006[35]
Upper tract[a]	0.002 (0.000-0.031)	Loo et al, 2013[2]; Feifer et al, 2010[20]; Lisanti et al, 2014[36]; Lang et al, 2002[37]
Men		
Lower tract	0.039 (0.000-0.109)	Loo et al, 2013[2]; Jung et al, 2011[16]
Upper tract[a]	0.004 (0.000-0.031)	Loo et al, 2013[2]; Jung et al, 2011[16]; Lang et al, 2002[37]
Smokers		
Lower tract	0.034 (0.000-0.064)	Loo et al, 2013[2]; Cumberbach et al, 2015[38]
Upper tract[a]	0.004 (0.000-0.031)	Cumberbach et al, 2015[38]; Lang et al, 2002[37]
Age ≥50 y		
Lower tract	0.031 (0.000-0.385)	Loo et al, 2013[2]; Jung et al, 2011[16]
Upper tract[a]	0.003 (0.000-0.042)	Loo et al, 2013[2]; Jung et al, 2011[16]
Ratio of RCC to UCC	12:2	Khadraetal,2000[39]
Computed Tomography		Helenius et al 2015[31]; Knox et al, 2008[33]; Lisanti et al, 2014[36]; Takeuchi et al, 2015[40]; Razavi et al, 2012[41]; Sadow et al, 2010[42]; Wang et al, 2009[43]; Sudakoff, 2008[44]; Cowan et al, 2007[45]; Helenius et al, 2016[46]; Sadow et al, 2008;[47] Wang et al, 2010[48]
Lower tract		
Sensitivity	0.950 (0.590-0.950)	Blick et al, 2012[24]; Sudakoff et al, 2008[44]; Helenius et al, 2016[46]
Specificity	0.830 (0.830-0.990)	Blick et al, 2012[24]; Helenius et al, 2015[31]
Upper tract		
Sensitivity	0.960 (0.818-0.970)	Razavi et al, 2012[41]; Sudakoff et al, 2008[44]; Cowan et al, 2007[45]; Chlapoutakis et al, 2010[49]
Specificity	0.990 (0.930-0.998)	Razavi et al, 2012[41]; Wang et al, 2009[43]; Sudakoff et al, 2008[44]; Chlapoutakis et al, 2010[49]
Cystoscopy		Blick et al, 2012[24]; Helenius et al, 2015[31]; Schmidbauer et al, 2009[50]
Lower tract		
Sensitivity	0.980 (0.870-0.980)	Blick et al, 2012[24]; Helenius, et al 2015[31]
Specificity	0.940 (0.940-1.000)	Blick et al, 2012[24]; Helenius, et al 2015[31]
Renal Ultrasound		Jaffe et al, 2001[26]; Knox et al, 2008[33]; Khadra et al, 2000[39]; Razavi et al, 2012[41]; Datta et al, 2002[51]; Yip et al, 1999[52]; Aslaksen et al, 1990[53]; Unsal et al, 2011[54]
Upper tract		
Sensitivity	0.910 (0.560-1.000)	Datta et al, 2002[51]; Aslaksen et al, 1990[53]; Unsal et al, 2011[54]; Speelman et al, 1996[55]
Specificity	0.990 (0.940-0.990)	Khadra et al, 2000[39]; Aslaksen et al, 1990[53]; Unsal et al, 2011[54]; Speelman et al, 1996[55]
Incidence of CIN following CT	0.040 (0.000-0.190)	Silver et al, 2015[12]; Marenzi et al, 2004[56]; Golshahi et al, 2014[57]
Incidence of UTI following cystoscopy	0.019 (0.000-0.030)	Herr, 2015[11]

Abbreviations: CIN, contrast-induced nephropathy; RCC, renal cell carcinoma; UCC, urothelial cell carcinoma; UTI, urinary tract infection.

[a] Includes both renal cell carcinoma and urothelial cell carcinoma of ureter and renal pelvis.

against its use for evaluation of AMH owing to poor sensitivity and minimal benefit.[20,23]

All strategies were evaluated relative to the reference case of performing no evaluation.

Clinical Data

Table 1 shows parameter estimates for clinical inputs abstracted from the literature. PubMed searches were performed to identify relevant literature for all key model inputs, including cancer incidence, diagnostic test accuracy, complications, and guideline compliance. For each model input, the clinical study with the most robust data and greatest applicability to the current model was selected as the primary model input. The remaining literature was utilized to generate ranges for sensitivity analysis. Cancer incidence among adult patients with AMH in the United States were obtained from Loo et al,[2] and incidence among high-risk groups (men, smokers, aged ≥50 years) were derived from the same cohort. Ranges for incidence among high-risk subgroups were obtained by inflating the incidence of cancer in the general population using relative risk of cancer among high-risk groups according to recent meta-analyses and population-based studies.[16,38]

Sensitivity and specificity of tests for upper and lower tract cancers were obtained from the literature. For strategies using multiple tests, we assumed no synergy between tests evaluating the same portion of the GU tract. For example, the sensitivity and specificity of the strategy combining CT and cystoscopy for detection of lower tract cancer was assumed equal to that of cystoscopy, which demonstrates higher accuracy.

Diagnosis of malignant abnormality was achieved with the first radiographic or pathologic evidence of disease. For radiographic diagnoses, morbidity and costs associated with confirmatory pathological diagnosis were considered

Table 2. Cost Inputs and Ranges Used in Sensitivity Analysis

Variable	CPT/HCPCS Code	Cost (Range), $[a]	References[b]
CT			
Urography	74178	356 (270-467)	MPFS
Renal	74176	202 (159-257)	MPFS
MRI renal protocol	74183	510 (381-678)	MPFS
Renal ultrasound	76770	115 (88-150)	MPFS
Cystoscopy	52000	208 (166-258)	MPFS
Cystoscopy + biopsy	52204	373 (286-480)	MPFS
Ureteroscopy	52351	313 (272-418)	MPFS
Ureteroscopy + biopsy	52354	430 (375-576)	MPFS
Biopsy pathology review	88305	74 (60-94)	MPFS
Incidental findings on CT	NA	409 (51-409)	Morgan et al, 2015[14]; Liu et al, 2005[58]
CIN after CT	NA	12 975 (6225-16 031)	Subramanian et al, 2007[13]
Clinic visit for UTI	99212	48 (35-55)	MPFS
Urinalysis and Urine culture	81001, 87086	15 (9-21)	MCLFS
Antibiotics for UTI	NA	8 (3-19)	Red Book[59]

Abbreviations: CIN, contrast-induced nephropathy; CPT, common procedural terminology; CT, computed tomography; HCPCS, Healthcare Common Procedure Coding System; MCLFS, Medicare Clinical Laboratory Fee Schedule 2016; MPFS, Medicare Physician Fee Schedule 2016; MRI, magnetic resonance imaging; UTI, urinary tract infection.

[a] All prices reported in 2016 US dollars.

[b] MPFS, Medicare Physician Fee Schedule 2016 at https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/PFSLookup/index.html?redirect=/pfslookup/; MCLFS, Medicare Clinical Laboratory Fee Schedule 2016 at https://www.cms.gov/medicare/medicare-fee-for-service-payment/clinicallabfeesched/clinlab.html.

Table 3. Incremental Cost per Cancer Detected (ICCD) for Diagnostic Strategies

Strategy	Cancers Detected[a]	Cost, $[a]	Δ Cancers	Δ Cost, $	ICCD, $
No evaluation	0	0	NA	NA	NA
CT only	221	9 300 000	221	9 300 000	Dominated
Cystoscopy only	222	2 284 000	222	2 284 000	10 287
Renal ultrasound + cystoscopy	245	3 504 400	23	1 220 400	53 810
CT + cystoscopy	246	11 540 200	1	8 035 800	6 480 484

Abbreviations: CT, computed tomography; ICCD, Incremental cost per cancer detected; NA, not applicable.

[a] Cancers detected and costs are reported as rate per 10 000 patients. Costs are reported in 2016 US dollars.

beyond the diagnostic window and thus excluded. False-positive findings on initial evaluation resulted in scenario-dependent confirmatory testing. Upper tract cancer on initial evaluation resulted in confirmatory testing consisting of ureteroscopy, CT, or magnetic resonance imaging (MRI) depending on the initial diagnostic modality. False-positive findings for lower tract cancer resulted in confirmatory testing consisting of cystoscopy and biopsy. False-negative findings (ie, undetected cancers) necessarily impacted the effectiveness of each strategy.

Complications and downstream consequences of each diagnostic evaluation were incorporated into the model. Cystoscopic interventions carried a 1.9% risk of febrile UTI, which required repeat urinalysis and urine culture, 1 additional clinic visit, and treatment with oral antibiotics.[11]

Cost Data

Cost inputs are presented in **Table 2**. All costs were evaluated from the payer perspective and updated to 2016 US dollars ($) using the medical care component of the Consumer Price Index.[60] Discounting was not used because the model time horizon was less than 1 year. National average nonfacility costs associated with diagnostic tests were obtained from the Medicare Physician Fee Schedule (MPFS) and the Medicare Clinical Laboratory Fee Schedule (MCLS).[61,62] Cost ranges for sensitivity analyses were obtained from the minimum and maximum Medicare reimbursement across all Medicare Administrative Contractor regions. Costs associated with pharmacologic treatment were obtained from the Red Book.[59] Additional costs secondary to incidental findings on CT or complications, such as CIN, were abstracted from the literature.[13,14]

Cost-effectiveness Analysis

Owing to the low prevalence of malignant abnormality associated with AMH, cost and effectiveness outcomes were scaled to a rate per 10 000 patients to optimize the possibility of detecting differences between strategies. Incremental analyses were performed by rank ordering strategies with increasing effectiveness relative to the reference strategy. Strategies that were dominated (ie, more costly and less effective) were removed, and an incremental cost per cancer detected (ICCD) was calculated for each strategy. Repeated analyses were performed for each of 3 subpopulations with unique risk of malignant abnormality (men, smokers, and age ≥50 years). We used a willingness-to-pay threshold of $100 000 per cancer detected and performed sensitivity analysis using thresholds of $50 000, $150 000, and $200 000.[63]

Additional sensitivity analyses were performed for all key variables to assess model stability. Probabilistic sensitivity analyses were performed using a triangular distribution with parameters determined by the aforementioned ranges. Additional head-to-head sensitivity analyses were performed for the 2 most optimal strategies according to ICCDs.

National Expenditures

The annual national expenditures secondary to AMH evaluation were estimated for the 2 guideline-endorsed strategies. We used the National Ambulatory Medical Care Survey (NAMCS) to determine the annual number of urologist visits with a diagnosis of AMH in 2012 (485 222). Additional national costs associated with use of CT in lieu of ultrasound were determined by factoring the number of visits by the cost difference between these 2 approaches, assuming 100% compliance with guidelines. Sensitivity analysis was performed using published and abstracted rates of guideline compliance.[2,64,65]

Results

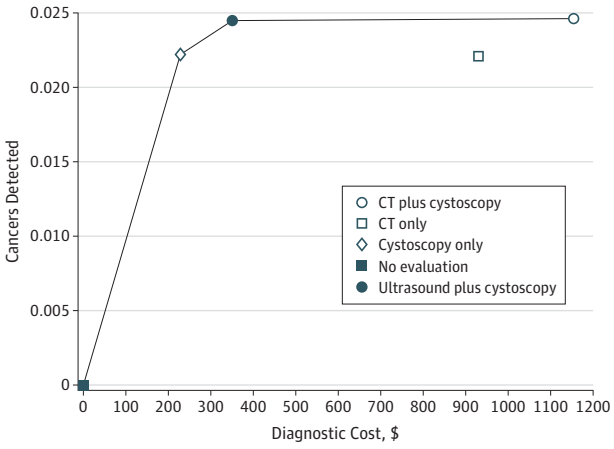
Base Case

Compared with no evaluation, CT alone detected the fewest additional cancers, 221 per 10 000 patients (**Table 3**). At a cost of $9 300 000 per 10 000 patients, the CT-alone strategy was dominated by all others (**Figure**). Cystoscopy alone detected 222 cancers at an ICCD of $10 287 compared with no evaluation. Addition of ultrasound resulted in the detection of 23 additional cancers at an ICCD of $53 810 compared with cystoscopy alone. Replacing ultrasound with CT detected just 1 additional cancer at an ICCD of $6 480 484, far exceeding the willingness-to-pay threshold.

On 1-way sensitivity analysis, the model was stable with variation of all inputs across the proposed ranges. A tornado diagram of inputs to which the ICCD was most sensitive in a head-to-head comparison of ultrasound and cystoscopy vs CT and cystoscopy is presented in the eFigure in the Supplement. Ultrasound and cystoscopy was the optimal strategy across all 1-way sensitivity analyses.

Our results were stable throughout a probabilistic sensitivity analysis using 1000 Monte Carlo simulations. The strategy of ultrasound and cystoscopy was optimal in 100% of simulations.

Figure. Cancers Detected and Costs of Diagnostic Protocols for Evaluation of Asymptomatic Microscopic Hematuria



CT indicates computed tomography.

Subgroup Analysis

Among high-risk groups, all strategies detected a greater number of cancers compared with the reference case (eTable in the Supplement). For men, smokers, and those aged 50 years or older, CT alone detected 382, 332, and 302 cancers per 10 000 patients, respectively. However, owing to high diagnostic costs, CT alone was dominated across all 3 groups. Cystoscopy alone detected 384, 334, and 303 cancers at ICCDs of $6047, $6918, and $7594, respectively, compared with no evaluation. The addition of ultrasound resulted in the detection of 39, 34, and 31 additional cancers for each high-risk group compared with cystoscopy alone. Replacing ultrasound with CT detected just 2 additional cancers in each group. The ICCDs for this strategy were more favorable (lower) than that of the base case but remained well above the willingness-to-pay threshold at $3 720 417, $4 297 326, and $4 727 059, respectively.

Our results were stable throughout a probabilistic sensitivity analysis using 1000 Monte Carlo simulations. The strategy of ultrasound and cystoscopy was optimal in 100% of simulations.

National Expenditures

In 2012, the diagnosis of microscopic hematuria was associated with 2.69% of patient visits to urologists, accounting for 485 222 visits. Assuming 100% urologist compliance with guidelines, use of CT instead of ultrasound would detect 60.2 additional cancers nationally at an incremental cost of $389 914 648 (**Table 4**). In the setting of imperfect compliance, use of CT instead of ultrasound would detect anywhere

Table 4. Projected Annual Additional National Costs and Cancers Detected With Use of Computed Tomography vs Ultrasound for Evaluation of Asymptomatic Microscopic Hematuria According to Rate of Compliance With Recommended Evaluation

Compliance, %	Additional Costs, $	Additional Cancers Detected	Cohort	Reference
100	389 914 648	60	Theoretical	NA
63	245 646 228	38	Patients who underwent CT evaluation	Loo et al, 2013[2]
49	191 058 177	30	Patients who underwent any imaging	Buteau et al, 2014[64]
36	140 369 273	22	Patients who underwent upper and lower tract evaluation	Shinagare et al, 2014[65]
5	19 495 732	3	Patients who underwent upper and lower tract evaluation	Buteau et al, 2014[64]

Abbreviations: CT, computed tomography; NA, not applicable.

from 3 to 38 additional cancers nationally at an incremental cost ranging from $19 495 732 to $245 646 228.

Discussion

While routine urinalysis for screening of GU malignant abnormalities is not presently recommended by any major health organization, hundreds of thousands of patients annually undergo urinalysis for various indications and are found to have microscopic hematuria prompting further evaluation. We found that the combination of renal ultrasound and cystoscopy was the most cost-effective approach for the evaluation of AMH. The superiority of this approach over the use of CT and cystoscopy is driven primarily by higher costs of CT and its associated complications, albeit rare. These costs were accompanied by minimal gains in cancer detection because ultrasound technology nearly reaches the sensitivity of CT for the detection of upper tract malignant abnormalities. Given the low prevalence of upper tract malignant abnormalities in patients with AMH, the small advantage in the sensitivity of CT imaging modalities does not compensate for the significant additional costs. Likewise, CT and cystoscopy was not a cost-effective first-line approach among patients with higher risk of malignant abnormality, because the absolute risk of malignant abnormality in this group remains low.

While ultrasound should be considered first-line, we urge clinicians to incorporate individualized patient-care and shared decision-making in the pursuit of follow-up CT or MRI. Though guidelines target optimal population-wide policy, patient preferences and risk factors must be considered on an individualized basis. Guidelines for the diagnosis and treatment of other GU malignant abnormalities, most notably prostate cancer, include shared decision-making as a central tenet.[66] Evaluation of AMH should follow this paradigm, because risk tolerance for CT-associated complications or uncertainty with regard to occult malignant abnormalities may vary. Furthermore, each clinical scenario may entail unique considerations or risk factors that have not been incorporated into the current model, such as family history of malignant abnormality, high number of RBCs on urinalysis, or presence of multiple risk factors.[16]

In the wake of the Affordable Care Act, the landscape of US health care has changed dramatically. Accountable care organizations (ACOs), along with other policy initiatives, continue to emphasize high-value and patient-centered care across all medical disciplines. In particular, diagnostic radiology has been recognized as an area ripe for transformation through stewardship and paradigm shifts.[67-69] Likewise, while surgeons and surgical care have been largely excluded from initial ACO models, recent authors have recognized that the integration of surgical care is paramount.[70,71] The prevalent condition of AMH sits at the crossroads of these 2 disciplines and offers an opportunity for the provision of high-value, individualized patient care.[9]

Implementation of ultrasound-based guidelines will substantially reduce national expenditures associated with AMH evaluation by up to $390 million. Although these reductions are rough estimates and do not account for the costs associated with delayed diagnosis of cancers that would have otherwise been detected by CT, they do represent a potential for large economic savings. In addition, the recommendation of ultrasound in lieu of CT may have the unintended but desirable consequence of improving compliance with hematuria evaluation. Studies[64,65] have demonstrated poor rates of urologic referral and compliance with hematuria evaluation among patients presenting to primary care physicians (PCPs). Prior authors have speculated that these low rates result from the unwillingness of PCPs to subject their patients to morbid evaluations, and the replacement of CT with ultrasound could therefore improve referral rates. Likewise, inclusion of PCPs in the development of future guidelines may help to ensure higher compliance, ultimately resulting in greater cancer detection.

Strengths and Limitations

Our study has a number of strengths. This is the first study to comprehensively model the effectiveness and costs of AMH evaluation in the era of modern imaging. Our findings are strengthened by the robust data inputs derived from extensive literature surrounding the incidence of cancer and accuracy of CT in AMH evaluation. Furthermore, stability of the model across all clinically determined ranges reinforces the findings and provides strong evidence for changing clinical practice.

However, our results must be interpreted in the context of the study design. First, the study is limited by the short model horizon, which prevented modeling the downstream effect of missed cancers on stage at presentation, life expectancy, quality of life, and costs. We chose the diagnostic period based on the lack of data on delayed diagnosis of bladder cancer, UTUC, and RCC. Second, owing to the heterogeneity of GU malignant abnormalities and the paucity of literature examining the impact of early detection on quality-adjusted life-years (QALY), we used the primary outcome of cancers detected in lieu of QALY as a measure of effectiveness. Although it is optimal for contextualizing population-based effects of AMH evaluation, this approach did not differentiate effectiveness and costs among patients with distinct types of GU cancers, nor did it model downstream costs of delayed cancer diagnosis. Whereas some studies have demonstrated poor outcomes among patients with delayed diagnosis of urothelial cancer, others have found that those with asymptomatic and symptomatic presentations had equivalent oncologic prognoses.[72,73] Third, limited data existed on accuracy of ultrasound for UTUC diagnosis. Though sensitivity analyses compensated for these data, further studies are needed to better determine the utility of ultrasound in this setting. Fourth, owing to limitations of NAMCS, estimates of national expenditures presume evaluation of all patients with microscopic hematuria, including symptomatic patients, which may inflate this estimate. Furthermore, we included only visits to urologists, which likely excluded a considerable number of patients who may undergo AMH evaluation by other providers (eg, gynecologists). This portion of the analysis is intended as an estimate for illustrative purposes and may not precisely capture national cost savings associated with distinct diagnostic

strategies, which would require more robust analysis with cost-driven data inputs. Fifth, the time horizon for our analysis could not account for the potential costs and morbidity associated with radiation from CT. On a population level over time, the incidence of secondary malignant abnormalities owing to radiation exposure would be substantial. As such, an ultrasound-based protocol would not only prove less costly in the long term, it would likely reduce overall morbidity secondary to radiation, thereby strengthening the case for ultrasound-based protocols from a policy perspective.[74,75] Sixth, incidence of CIN was abstracted from a review evaluating percutaneous coronary intervention, which likely overestimates incidence for CT owing to lower contrast requirement. However, this estimation was accounted for in sensitivity analysis and did not change model outcomes.[12] Finally, MR urography was not evaluated as an initial diagnostic evaluation owing to high costs and inadequate access. However, MRI offers the advantage of high sensitivity without radiation exposure and may be optimal for specific patients.[76]

Conclusions

The combination of ultrasound and cystoscopy is the most cost-effective among 4 diagnostic approaches for the initial evaluation of AMH. The use of ultrasound in lieu of CT as the first-line diagnostic strategy will reduce the cost, morbidity, and national expenditures associated with evaluation of AMH. Clinicians and policy makers should consider changing future guidelines in accordance with this finding.

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Concept and design: All authors.
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Drafting of the manuscript: Halpern, Chughtai.
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Supplementary Online Content

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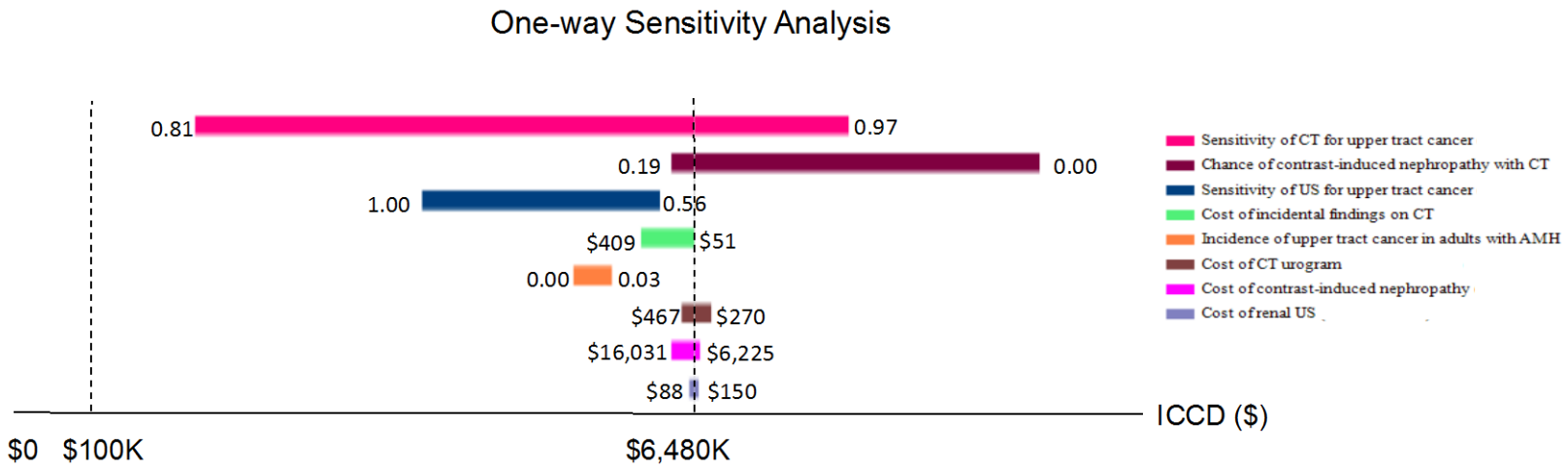
This supplementary material has been provided by the authors to give readers additional information about their work.

eTable: Incremental Cost per Cancer Detected (ICCD) For Diagnostic Strategies Among Subgroups

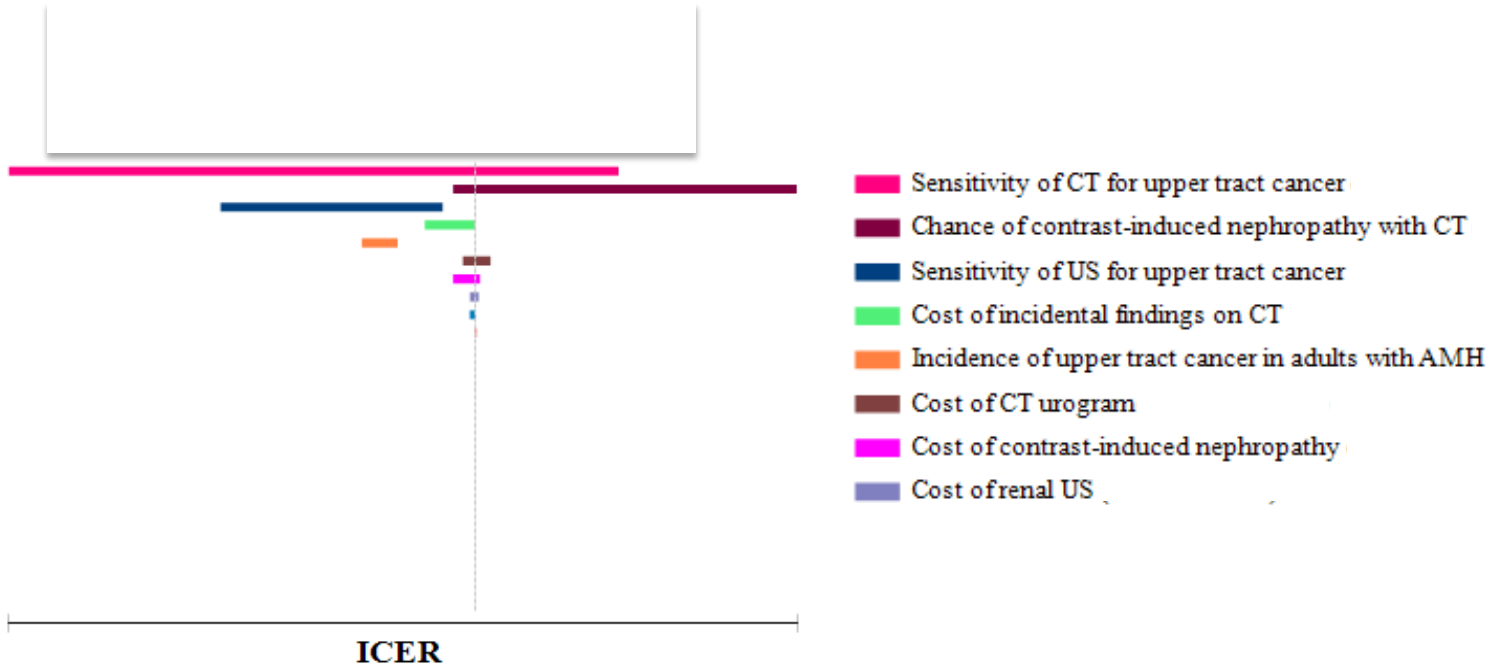
	Males			Smokers			Age > 50		
Strategy	**Δ cancers**	**Δ cost**	**ICCD**	**Δ cancers**	**Δ cost**	**ICCD**	**Δ cancers**	**Δ cost**	**ICCD**
No evaluation	-	-	-	-	-	-	-	-	-
CT only	382	$9,298,200	Dominated	332	$9,298,700	Dominated	302	$9,299,100	Dominated
Cystoscopy only	384	$2,320,200	$6,047	334	$2,309,000	$6,918	303	$2,302,200	$7,594
US + cystoscopy	39	$1,219,100	$31,107	34	$1,219,500	$35,773	31	$1,219,700	$39,383
CT + cystoscopy	2	$8,036,100	$3,720,417	2	$8,036,000	$4,297,326	2	$8,036,000	$4,727,059

*Cancers detected and costs are reported as rate per 10,000 patients
CT = computed tomography; US = renal ultrasound; dominated = less effective and more expensive than another intervention;

eFigure.



Note: US and cystoscopy remained the optimal strategy across all one-way sensitivity analysis, as ICCD for CT and cystoscopy was above the $100K willingness-to-pay threshold throughout
ICCD = incremental cost per cancer detected; K = thousand



eFigure 1: Incremental cost-effectiveness ratio (ICER) tornado diagram for comparison of computed tomography (CT) and cystoscopy versus ultrasound (US) and cystoscopy