Assessment of a clinical pathway for investigation of haematuria that reduces the need for cystoscopy

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ABSTRACT

AIM: To evaluate prospectively a clinical pathway for investigation of haematuria that involves an initial screening using a urinary biomarker of bladder cancer (Cxbladder Triage™ (CxbT)) in combination with either a renal ultrasound or a computed tomography imaging. Only test-positive patients are referred for specialist assessment and flexible cystoscopy.

METHODS: The clinical outcomes of 884 patients with haematuria who presented to their general practitioner were reviewed. Outcome measurements included the findings of laboratory tests, imaging, cystoscopies, specialist assessment and histology.

RESULTS: Forty-eight transitional cell carcinomas (TCC) and three small cell carcinomas were diagnosed in the study cohort. The clinical pathway missed a solitary, small, low-risk TCC. When combined, imaging and CxbT had a sensitivity of 98.1% and a negative predictive value of 99.9% to detect a bladder cancer. Follow-up for a median of 21 months showed no further new cases of bladder cancer had occurred in the patient cohort. Review of all new bladder cancers diagnosed in the 15 months following the study showed that none had been missed by haematuria assessment using the clinical pathway.

CONCLUSIONS: The combination of CxbT and imaging reliably identifies patients with haematuria who can be managed safely in primary care without the need for a secondary care referral and a flexible cystoscopy.

In an earlier issue of the *New Zealand Medical Journal*, we described the development of a clinical pathway for the investigation of patients with haematuria.[1] The pathway used imaging and a urinary biomarker assay of bladder cancer (Cxbladder Triage™ (CxbT)) to identify patients who required a referral for specialist assessment to exclude the possibility of a bladder malignancy (refer to Appendix). The imaging modality requested depended on the type of haematuria and the age of the patient: renal ultrasound for microhaematuria and patients <40 and >85 years of age with macrohaematuria, and intravenous computed tomography (IVU-CT) for all other cases of macrohaematuria. The pathway did not include urine cytology in the initial laboratory screening tests and used the high negative predictive potential of CxbT combined with appropriate imaging to identify patients who did not require a secondary care appointment and flexible cystoscopy. Patients were only referred for urological assessment and cystoscopy if their CxbT index was positive and/or their imaging showed a bladder or other urinary-tract abnormality. Urine cytology could be requested at this stage at the discretion of the urologist. Patients with persistent microhaematuria, a urine total

albumin:creatinine ratio >70, an eGFR <60 ml/min/1.73m^2 or newly diagnosed hypertension were referred to a nephrologist for evaluation. The pathway was a departure from international clinical guidelines that recommend cystoscopy as the gold standard for diagnosis of bladder cancer.[2,3] A previous retrospective analysis of a cohort of patients with haematuria showed that the clinical pathway would have detected all invasive urothelial carcinomas and that approximately one-third of patients could have safely avoided the need for an invasive flexible cystoscopy with negligible risk of a bladder cancer being missed.[1]

Since February 2018, patients with haematuria in the Canterbury region have been investigated under the guidelines of the new clinical pathway. To inform general practices of these changes, the pathway was made available on the Canterbury Community HealthPathways website.[4] A clinical review of the effectiveness and safety of the new pathway was carried out prospectively during the first year of its introduction. This paper reports the findings of this review.

Patients and methods

The Health and Disability Ethics Committee, Ministry of Health, New Zealand, advised that the clinical review did not require ethical approval, as it constituted monitoring and improvement of usual patient care carried out by the Canterbury District Health Board (CDHB).

Patients

The clinical records of 889 patients who had a CxbT test for investigation of haematuria between 1 February 2018 and 31 January 2019 were reviewed. Five patients were excluded from the analysis: one with a bleed from a catheter, and four because of inadequate information on their medical records, two of whom had declined their hospital appointment.

Within the CDHB region there is a population of 567,870 (2018/19 projection). A single group of urologists provide urological services to all patients within the CDHB region, in both the public and private sectors. Thus, the patients described in this paper represent a nearly complete community capture.

Data collection

Data was collected on the remaining 884 patients in a non-blinded manner and included: demographic characteristics, type of haematuria, presence of risk factors for bladder cancer (smoking, previous history of bladder cancer and radiation therapy of the pelvis) and the findings of laboratory tests, imaging, cystoscopies, specialist assessment and histology. A cystoscopy and histology were required for diagnosis of bladder cancer. Macrohaematuria was defined as blood clearly visible in a midstream urine sample, and microhaematuria was defined as >20x10^{6}L red blood cells in two of three samples collected seven days apart.

A follow-up review (median: 21 months; range: 16–27 months) was then carried out of all the patients who had not been diagnosed with bladder cancer to ensure that no malignancy had been missed. The patients' electronic records of inpatient admissions, outpatient clinics and histology results, and a search of the New Zealand Cancer Registry, were included in this review.

Finally, all the new diagnoses of bladder cancer in the CDHB region for a subsequent 15-month period from 1 February 2019 to 30 April 2020 were identified from surgical and pathology records. The patient records were reviewed to see whether any of these patients had previously been investigated by the new pathway for haematuria and had a bladder cancer missed.

Statistical analysis

The flow of patients through the three arms of the clinical pathway, grouped according to whether they had microhaematuria, macrohaematuria or were aged <40yr or >85, was examined graphically. The diagnostic accuracy of the various investigations in the pathway to detect bladder cancer was determined by calculation of accuracy, sensitivity, specificity and negative predictive value (NPV). The evaluation of CxbT used a segregation index cut-off value of <4.0 to indicate specialist assessment was required.[5]

Statistical power analysis showed that at least 600 patients would allow a precise estimate of the diagnostic accuracy of the indices, assuming a target sensitivity of 90% and a precision of sensitivity measurement

of 10%, and given the prevalence of bladder cancer observed in the review patient cohort of 5.8%.

Results

The clinical and demographic characteristics of the 884 patients are summarised in Table 1. All the patients lived in the funded area of the Canterbury DHB and were predominantly middle-aged or older, with 66% being male. Two-thirds of the patients presented with macrohaematuria. Approximately 43% of the patients were classified as having an increased risk of developing bladder cancer because of their smoking history (41%), a previous history of bladder cancer (0.001%) or having previously received radiation therapy of the pelvis (2%).

Table 1: Demographic and clinical characteristics of the 884 patients.

Parameter	
Male	584 (66%)
Female	300 (34%)
Age (years)	
Mean (±SD)	63.1 (16.2)
Median (range)	65 (14–97)
Type of haematuria	
Macrohaematuria	566 (64%)
Microhaematuria	318 (36%)
Smoking status	
Current smoker	71 (8%)
Previous smoker	293 (33%)
Never smoked	520 (59%)
Ethnicity	
NZ European	719 (81%)
Māori	23 (3%)
Pacific Islander	7 (1%)
Asian	43 (5%)
MELAA[a]	11 (1%)
Not stated	81 (9%)
Previous clinical history	
Bladder cancer	1 (0.001%)
Radiation therapy of pelvis[b]	21 (2%)

[a]Middle Eastern/Latin American/African.
[b]Prostate n=19, rectum n=2.

The flow of the patients through the three arms of the clinical pathway and the diagnoses for the cause of haematuria are shown in Figure 1. One hundred and seventeen patients were still referred to a specialist urologist despite their CxbT being normal and their imaging indicating no bladder cancer was present. Seventy patients were diagnosed with another urological condition, while in 47 cases the cause of haematuria could not be identified.

The clinical pathway detected all but one case of bladder cancer, with 48 patients (macrohaematuria: n=44; microhaematuria: n=4) diagnosed with a histologically confirmed (n=46), or clinically possible (n=2), transitional cell carcinoma (TCC) and three with a small cell carcinoma. The stage and grade of the 48 TCCs were low grade (pTa n=20 and CIS n=1), and high grade (pTa n=14, pT1 n=8 and pT2 n=3). Two further malignancies were designated cT2-3, as neither had a cystoscopy or histology (one was frail and 91 years old, and the other had widespread metastatic bowel cancer). The 51 cases of bladder cancer represented a prevalence rate of 5.77%.

Three hundred and forty-eight (39%) patients with haematuria and normal CxbT and radiology were managed in primary care alone. Two hundred and eighty-nine patients had a sample collected for urine cytology, with 64% of these requests made by a urologist at the time of the hospital clinic visit.

The ability of CxbT, imaging and the combination of CxbT and imaging to detect bladder cancer and the diagnostic accuracy of these investigations in the study cohort are summarised in Table 2. Five cancers were missed by CxbT. One of these was a superficial, high-grade lesion (pTaHG, 1cm in size). A second was considered from cytology to be high grade, but clinically it was thought to be most likely of bowel origin in a patient with extensive metastatic bowel cancer. No cystoscopy was performed, nor was a histology taken, in this patient. The other three cancers were low-grade pTa lesions. Although CxbT had relatively high

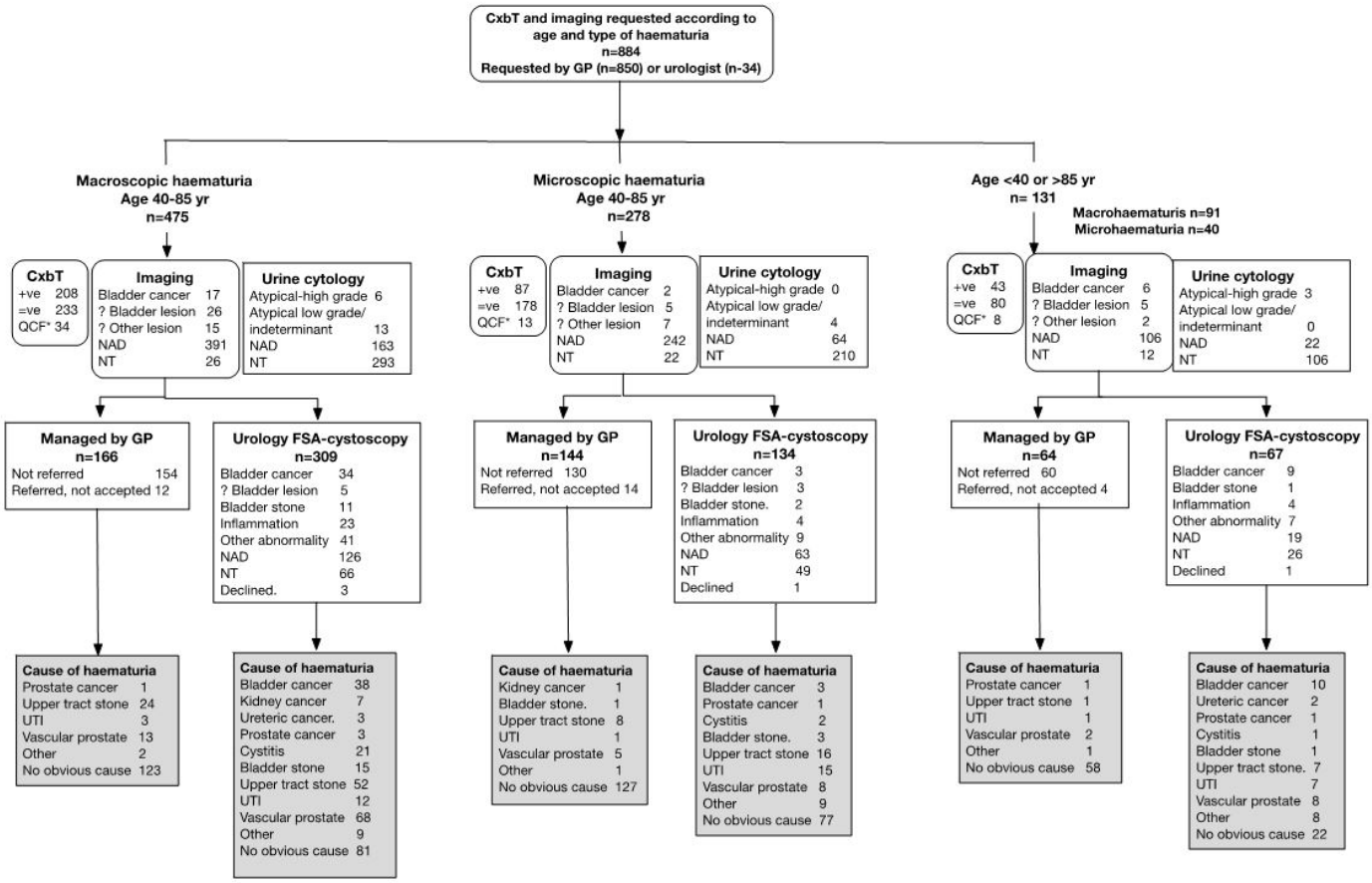
sensitivity to detect a bladder cancer and a high NPV of 98.9% to exclude the possibly of a lesion, the test had a low specificity with 39% of the tests returning a false-positive result. This level of diagnostic accuracy for CxbT is similar to that reported previously.[6–8] The mean of the CxbT segregation index was 3.97 (SD=0.92; range: 1.97–10.0), with 466 patients (53%) having a score less than the triage cut-off of 4.0. Approximately 10% of the patients (85 of 884) required a repeat CxbT assay because of quality control failures, mainly caused by interference of inflammatory products or a large number of white blood cells. Of these 85 patients, the repeat test provided a result in 28, and the second test did not meet quality standards in 15, while a repeat test was not requested in 42.

Imaging failed to detect 13 lesions (ultrasound: n=7; CT-IVU: n=5; ultrasound + CT-IVU: n=1), with nine of these lesions classified as low-grade lesions (pTa) and four as high-grade lesions (pT1: n=3; assessed by cytology: n=1). When combined, the pathway of CxbT and imaging had a sensitivity of 98.1% and an NPV of 99.9% and failed to detect a solitary, small, low-grade pTa bladder cancer.

Flexible cystoscopy detected bladder cancer in 48 patients, while the remaining three cancers were observed subsequently by rigid cystoscopy carried out at the time of transurethral resection of a bladder tumour (TURBT). One patient with widespread metastatic disease from bowel cancer did not have a cystoscopy.

Table 3 summarises the causes of haematuria and the percentage of each cause detected by the clinical pathway. Renal stones, vascular prostate and inflammatory conditions were the most common causes of haematuria. Inflammatory renal disease was the cause of microhaematuria in six cases, all of whom were referred to a nephrologist for management.[3] In approx-

Figure 1: Flow of the 884 patients through the three arms of the haematuria clinical pathway.



QCF: quality control failure; FSA: first specialist assessment; NAD: no abnormality detected; NT: not tested.

imately one-third of patients, the cause of haematuria was not determined.

Follow-up review of medical records of the 833 patients who had not been diagnosed with bladder cancer showed that one patient had been treated for a small papillary lesion on the bladder neck six months following a nephroureterectomy for a high-grade TCC of the kidney. No other patient had been admitted to hospital for management of a new bladder malignancy. A search of the New Zealand Cancer Registry confirmed this finding.

A review of all the subsequent bladder cancers diagnosed in the following 15 months identified 111 patients with a first diagnosis of bladder cancer, confirmed histologically. Seventy-one percent were identified through GP workup of haematuria, 23% incidentally through radiology, 2% incidentally through cystoscopy and 4% through secondary care investigation of haematuria. Of those coming through the GP workup of haematuria, 42 (53%) had a successful CxbT test and eight had a "quality control" failure of the test. Two

Table 2: Evaluation of the diagnostic accuracy of CxbT, imaging and cystoscopy to detect bladder cancer. The diagnostic parameters are expressed as percentages (95% confidence interval).

	Bladder cancer diagnosis (n=51)	**Diagnostic parameters**			
		Accuracy	**Sensitivity**	**Specificity**	**Negative predictive value**
Cxbladder triage		60.7% (57.3–64.1%)	89.4% (76.9–96.5%)	59.0% (55.4–62.4%)	98.9% (97.5–99.5%)
Bladder cancer indicated	41				
Bladder cancer not indicated	5				
Quality control failure	5				
Ultrasound		96.3% (94.0–97%)	65.2% (42.7–83.6%)	98.2% (96.3–99.3%)	97.9% (96.3–98.8%)
Bladder cancer detected	12				
Possible bladder cancer	3				
No bladder cancer detected	8				
Not tested	28				
CT-IVU		95.5% (93.4–97.1%)	81.6% (65.7–92.3%)	96.4% (94.4–97.9%)	98.8% (97.8–99.4%)
Bladder cancer detected	19				
Possible bladder cancer	12				
No bladder cancer detected	6				
Not tested	14				
Cxbladder Triage + imaging		98.4% (97.4–99.1%)	98.1% (89.6–99.9%)	98.4% (97.3–99.2%)	99.9% (99.2–99.9%)
Bladder cancer detected	47				
Possible bladder cancer	3				
No bladder cancer detected	1				

Table 3: Causes of haematuria in the study cohort.

	Male n=583		**Female n=301**	
Malignant lesions				
Bladder cancer	40	(6.9%)	11	(3.7%)
Kidney cancer TCC[a]	4	(0.7%)	-	-
Kidney cancer RCC[b]	1	(0.2%)	2	(0.7%)
Ureter cancer	3	(0.5%)	2	(0.7%)
Prostate cancer	5	(0.9%)	-	-
Inflammatory				
Urinary tract infection	15	(2.6%)	19	(6.3%)
Cystitis	19	(3.3%)	5	(1.7%)
Stones				
Upper tract	51	(8.7%)	24	(8.0%)
Bladder	18	(3.0%)	1	(0.3%)
Other causes				
Vascular prostate	81	(13.9%)	-	-
Anticoagulation	11	(1.9%)	1	(0.3%)
Renal disease	5	(0.8%)	-	
Catheter	3	(0.5%)	1	(0.3%)
Post-TURP	2	(0.3%)	-	
Exercise-induced	1	(0.2%)	1	(0.3%)
Urethral stricture	1	(0.2%)	-	
Urethral caruncle	-		1	(0.3%)
Primary amyloidosis	1	(0.2%)	-	
Endometriosis	-	-	1	(0.3%)
No cause identified	116	(19.9%)	64	(21.3%)
Not referred	179	(30.7%)	156	(51.9%)
Referred, not accepted	21	(3.6%)	8	(2.6%)
Referred, accepted, but patient declined	6	(1.0%)	4	(1.3%)

[a]Transitional cell carcinoma. [b]Renal cell carcinoma.

patients had a CxbT test that was <4 and a suspicious radiology. Both were found to have low-grade pTa malignancies. Only one patient had a bladder cancer missed in an earlier workup of haematuria. This patient had an ultrasound, but no CxbT, and a flexible cystoscopy that showed no abnormality. The cystoscopy was repeated three months later due to continued haematuria and the cancer was found.

Discussion

Successful treatment of invasive bladder cancer relies on early detection of the malignancy. Flexible cystoscopy supported by the findings of imaging and urine cytology have been the "gold standard" diagnostic procedures for investigation of patients with haematuria and a possible bladder cancer.[2,3] However, the invasive nature of cystoscopy and its relatively poor cost performance,[9] coupled with the low diagnostic accuracy of cytology for low-grade bladder cancers, emphasises the need for an improved clinical approach for investigation of haematuria.[10] To this end, over the last 10 years a large number of urinary biomarkers have been developed and assessed for the diagnosis and monitoring of bladder cancer.[11–14] The range and type of these biomarkers reflects the complex aetiology and development of bladder cancer, with assay profiles based on either the levels or presence of specific microRNAs,[15,16] proteins,[17] metabolites[18] or extracellular vesicals.[12] Despite extensive evaluation, none of these molecular biomarkers are included in clinical guidelines or recommended for use in daily clinical practice.[16,19–22]

The clinical pathway for investigation of haematuria evaluated in this paper was developed against this background and included the addition of CxbT in the initial laboratory investigations. This assay measures the level of five miRNAs to calculate a segregation index for stratification of patients.[6,7] miRNAs are promising candidates for the diagnosis of bladder cancer as they are involved in several processes associated with the development of these malignancies, including proliferation, invasion, migration and apoptosis.[23] Evaluation of the pathway during its development showed that CxbT improved the risk stratification of patients with haematuria and identified those in whom it was safe not to undertake cystoscopy.[1] The prospective review of the pathway and follow-up of the patients described in this paper confirmed that the clinical pathway was an effective clinical algorithm for investigation of haematuria and that it reliably identified patients with bladder cancer. Interestingly, the 5.8% prevalence of bladder cancer in the current review was lower than that observed in the patient cohort used for development of the clinical pathway (9.2%).[1] The reasons for this difference may be natural variation, an increased awareness of haematuria due to the communication around the change to the HealthPathway, or as a consequence of the relatively small size of the patient cohorts. We are currently carrying out reviews of the cost effectiveness, equity of access to haematuria assessment and compliance with the clinical pathway.

The risk of avoiding a cystoscopy is the possibility of missing a significant bladder cancer. Our results showed a false-negative CxbT result was obtained in five of the 52 patients diagnosed with bladder cancer, with one of these being a superficial (pTa) high-grade lesion, one likely to be a metastasis from a bowel cancer,not a transitional cell malignancy, and with the remaining three being low-grade pTa malignancies. Imaging detected the bladder cancer in four of these patients, while in the remaining patient a small, low-risk cancer (pTaLG) was detected three months later by cystoscopy following continued haematuria. These findings emphasise that an accurate risk stratification of patients with haematuria cannot be achieved using a urinary biomarker alone, and that the use of these tests in clinical pathways must be supported by appropriate imaging.

The adoption of the haematuria assessment pathway allowed 39% of patients to be fully cared for in primary practice, thus avoiding referral to secondary care. While this benefits the patient and the system, it is important to be certain that the clinical risk to the patient is not increased. Of the 884 haematuria patients undertaking the pathway (CxbT and radiology), only a single low-risk (low-grade pTa) cancer was missed. The NPV of 99.9% is consistent

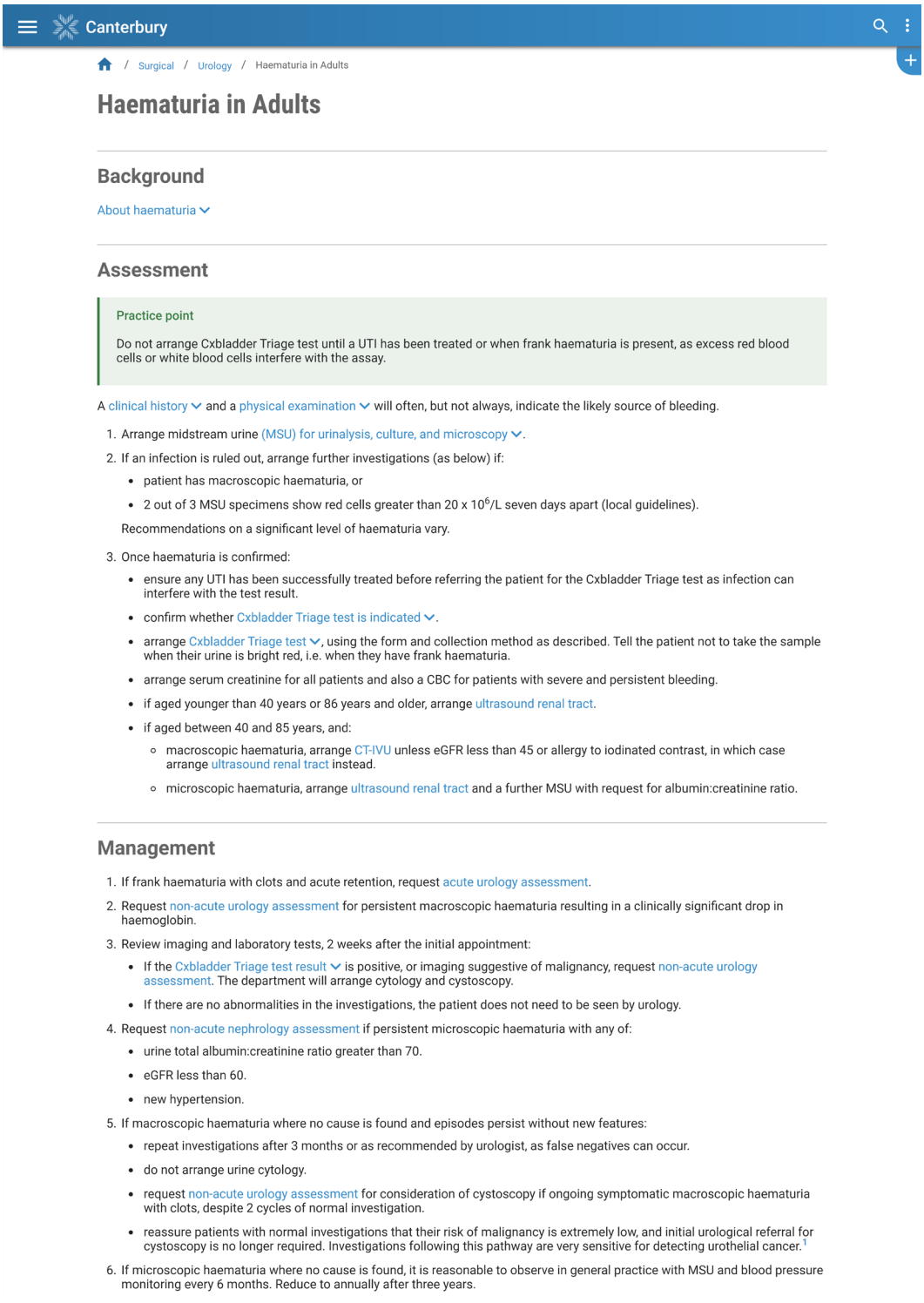
with previously published results.[1,5] The follow-up review of the clinical records of the 832 patients who did not have a bladder cancer detected by the new pathway identified a single similar low-risk cancer in a follow-up cystoscopy of a patient in whom the pathway had previously diagnosed an upper tract transitional cell malignancy. In addition, a review of all the newly diagnosed bladder cancers in the CDHB region over the following 15 months identified only one bladder cancer missed during a previous haematuria investigation. The haematuria investigation in this case had not followed the "pathway", and had not had a CxbT, but did have a cystoscopy that did not identify the cancer. Therefore, it is concluded that patients with haematuria and a negative "pathway" workup (CxbT and radiology) have a negligible clinical risk of missing a significant bladder cancer.

Finally, the argument could be made that there are other significant causes of haematuria. Of these, upper tract tumours and urinary tract stones are the most significant. These are readily identified on radiology as a part of the haematuria pathway. When evaluating the findings of the follow-up review of approximately 21 months, it is important to take into account that the development of non-invasive papillary carcinomas is relatively slow[24] and may vary according to tumour grade and stage.[24,25] It is therefore possible that a lesion may not have been identified within this time period.

In conclusion, we are not aware of any other study that has prospectively assessed the inclusion of a urinary biomarker to improve the risk stratification of patients with haematuria. The findings of our study add to the increasing evidence that biomarkers have a place in the assessment of haematuria, but that the results of these assays need to be supported by imaging of the bladder. Our study demonstrates that, when they are provided with CxbT results in combination with imaging, clinicians are able to reliably identify patients who can be assessed in primary care without the need for a secondary care referral and a flexible cystoscopy. We consider that in a well-integrated health system the management of these test-negative patients can be safely undertaken by general practitioners with support and oversight provided by a specialist urologist.

Appendix

Appendix Figure 1: Extract from Canterbury Community HealthPathways used by general practice for locally agreed guidance on over 800 conditions and situations. Each piece of underlined blue text represents a dropdown providing further clinical and process information.



Canterbury

/ Surgical / Urology / Haematuria in Adults

Haematuria in Adults

Background

About haematuria

Assessment

Practice point

Do not arrange Cxbladder Triage test until a UTI has been treated or when frank haematuria is present, as excess red blood cells or white blood cells interfere with the assay.

A clinical history and a physical examination will often, but not always, indicate the likely source of bleeding.

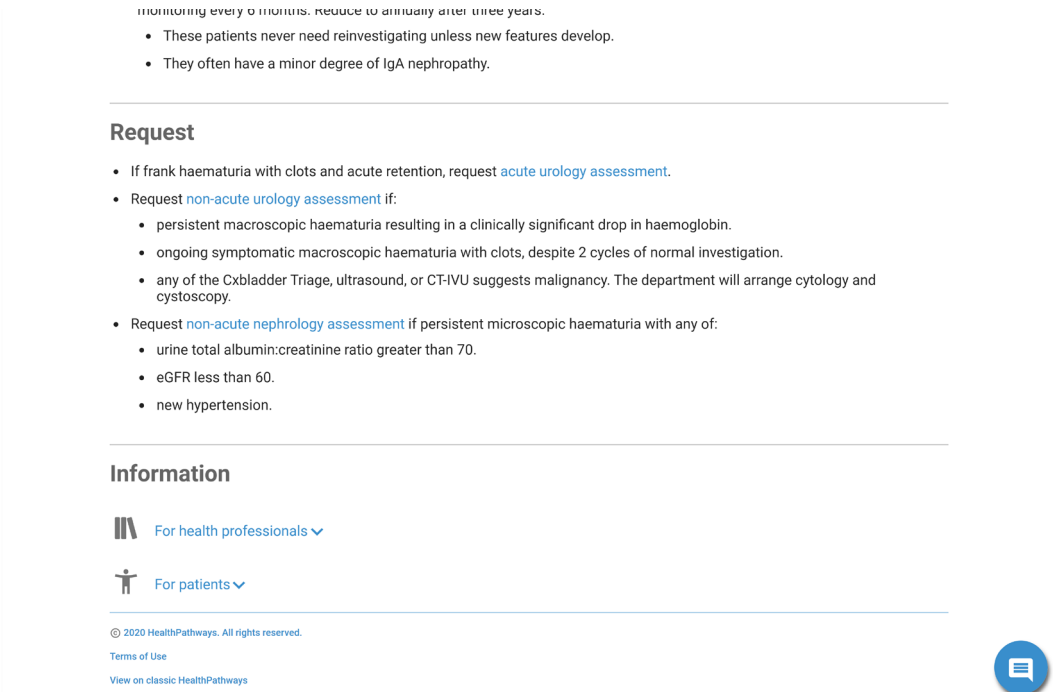
1. Arrange midstream urine (MSU) for urinalysis, culture, and microscopy.
2. If an infection is ruled out, arrange further investigations (as below) if:
   - patient has macroscopic haematuria, or
   - 2 out of 3 MSU specimens show red cells greater than 20 x 10^6/L seven days apart (local guidelines).

   Recommendations on a significant level of haematuria vary.
3. Once haematuria is confirmed:
   - ensure any UTI has been successfully treated before referring the patient for the Cxbladder Triage test as infection can interfere with the test result.
   - confirm whether Cxbladder Triage test is indicated.
   - arrange Cxbladder Triage test, using the form and collection method as described. Tell the patient not to take the sample when their urine is bright red, i.e. when they have frank haematuria.
   - arrange serum creatinine for all patients and also a CBC for patients with severe and persistent bleeding.
   - if aged younger than 40 years or 86 years and older, arrange ultrasound renal tract.
   - if aged between 40 and 85 years, and:
     - macroscopic haematuria, arrange CT-IVU unless eGFR less than 45 or allergy to iodinated contrast, in which case arrange ultrasound renal tract instead.
     - microscopic haematuria, arrange ultrasound renal tract and a further MSU with request for albumin:creatinine ratio.

Management

1. If frank haematuria with clots and acute retention, request acute urology assessment.
2. Request non-acute urology assessment for persistent macroscopic haematuria resulting in a clinically significant drop in haemoglobin.
3. Review imaging and laboratory tests, 2 weeks after the initial appointment:
   - If the Cxbladder Triage test result is positive, or imaging suggestive of malignancy, request non-acute urology assessment. The department will arrange cytology and cystoscopy.
   - If there are no abnormalities in the investigations, the patient does not need to be seen by urology.
4. Request non-acute nephrology assessment if persistent microscopic haematuria with any of:
   - urine total albumin:creatinine ratio greater than 70.
   - eGFR less than 60.
   - new hypertension.
5. If macroscopic haematuria where no cause is found and episodes persist without new features:
   - repeat investigations after 3 months or as recommended by urologist, as false negatives can occur.
   - do not arrange urine cytology.
   - request non-acute urology assessment for consideration of cystoscopy if ongoing symptomatic macroscopic haematuria with clots, despite 2 cycles of normal investigation.
   - reassure patients with normal investigations that their risk of malignancy is extremely low, and initial urological referral for cystoscopy is no longer required. Investigations following this pathway are very sensitive for detecting urothelial cancer.[1]
6. If microscopic haematuria where no cause is found, it is reasonable to observe in general practice with MSU and blood pressure monitoring every 6 months. Reduce to annually after three years.

Appendix Figure 1: Extract from Canterbury Community HealthPathways used by general practice for locally agreed guidance on over 800 conditions and situations. Each piece of underlined blue text represents a dropdown providing further clinical and process information (continued).



monitoring every 6 months. Reduce to annually after three years.

- These patients never need reinvestigating unless new features develop.
- They often have a minor degree of IgA nephropathy.

Request

- If frank haematuria with clots and acute retention, request acute urology assessment.
- Request non-acute urology assessment if:
  - persistent macroscopic haematuria resulting in a clinically significant drop in haemoglobin.
  - ongoing symptomatic macroscopic haematuria with clots, despite 2 cycles of normal investigation.
  - any of the Cxbladder Triage, ultrasound, or CT-IVU suggests malignancy. The department will arrange cytology and cystoscopy.
- Request non-acute nephrology assessment if persistent microscopic haematuria with any of:
  - urine total albumin:creatinine ratio greater than 70.
  - eGFR less than 60.
  - new hypertension.

Information

For health professionals

For patients

Terms of Use

View on classic HealthPathways

Competing interests:
Nil.
Acknowledgements:
Review of the clinical pathway for investigation of haematuria was conducted as part of the improvement of usual patient care by the Canterbury DHB who purchased the test kits and paid for analysis by Pacific Edge Ltd, who otherwise played no part in the study. The samples were collected using the usual methods of general practice testing and we would like to acknowledge the general practice teams and patients who diligently collected the samples. The authors acknowledge the assistance of Canterbury Southern Community Laboratories in the collection and administration of the CxbT samples and collation of the assay results. We are also grateful to Mrs Timi Boddington, Information Analyst, Planning and Funding, Canterbury DHB, and to Mrs Barbara Gordon and Mrs Liz Mitchell from the Canterbury Urology Research Trust for carrying out the follow-up reviews of the patients' medical records, and to Ma Yi, Biostatistician, Canterbury DHB for assistance with the statistical analyses.
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www.nzma.org.nz/journal-articles/assessment-of-a-clinical-pathway-for-investigation-of-haematuria-that-reduces-the-need-for-cystoscopy-open-access

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