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The research reported in this monograph was commissioned by the HTA Programme as project number 02/01/01. The contractual start date was in September 2003. The draft report began editorial review in February 2005 and was accepted for publication in September 2005. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

Diagnostic tests and algorithms used in the investigation of haematuria: systematic reviews and economic evaluation

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Objectives: To determine the most effective diagnostic strategy for the investigation of microscopic and macroscopic haematuria in adults.
Data sources: Electronic databases from inception to October 2003, updated in August 2004.
Review methods: A systematic review was undertaken according to published guidelines. Decision analytic modelling was undertaken, based on the findings of the review, expert opinion and additional information from the literature, to assess the relative cost-effectiveness of plausible alternative tests that are part of diagnostic algorithms for haematuria.
Results: A total of 118 studies met the inclusion criteria. No studies that evaluated the effectiveness of diagnostic algorithms for haematuria or the effectiveness of screening for haematuria or investigating its underlying cause were identified. Eighteen out of 19 identified studies evaluated dipstick tests and data from these suggested that these are moderately useful in establishing the presence of, but cannot be used to rule out, haematuria. Six studies using haematuria as a test for the presence of a disease indicated that the detection of microhaematuria cannot alone be considered a useful test either to rule in or rule out the presence of a significant underlying pathology (urinary calculi or bladder cancer). Forty-eight of 80 studies addressed methods to localise the source of bleeding (renal or lower urinary tract). The methods and thresholds described in these studies varied greatly, precluding any estimate of a 'best performance' threshold that could be applied across patient groups. However, studies of red blood cell morphology that used a cut-off value of 80% dysmorphic cells for glomerular disease reported consistently high specificities (potentially useful in ruling in a renal cause for haematuria). The reported sensitivities were generally low. Twenty-eight studies included data on the accuracy of laboratory tests (tumour markers, cytology) for the diagnosis of bladder cancer. The majority of tumour marker studies evaluated nuclear matrix protein 22 or bladder tumour antigen. The sensitivity and specificity ranges suggested that neither of these would be useful either for diagnosing bladder cancer or for ruling out patients for further investigation (cystoscopy). However, the evidence remains sparse and the diagnostic accuracy estimates varied widely between studies. Fifteen studies evaluating urine cytology as a test for urinary tract malignancies were heterogeneous and poorly reported. The calculated specificity values were generally high, suggesting some possible utility in confirming malignancy. However, the evidence suggests that urine cytology has no application in ruling out malignancy or excluding patients from further investigation. Fifteen studies evaluated imaging techniques [computed tomography (CT), intravenous urography (IVU) or ultrasound scanning (US)] to detect the underlying cause of haematuria. The target condition and the reference standard varied greatly between these studies. The diagnostic accuracy data for several individual studies appeared promising but meaningful comparison of the available imaging technologies was impossible. Eight studies met the inclusion criteria but addressed different parts of the diagnostic chain (e.g. screening programmes, laboratory investigations, full urological work-up). No single study addressed the complete diagnostic process. The review also highlighted a number of methodological limitations of these studies, including their lack of generalisability to the UK context. Separate decision analytic models were therefore developed to progress estimation of the optimal strategy for the diagnostic management of

haematuria. The economic model for the detection of microhaematuria found that immediate microscopy following a positive dipstick test would improve diagnostic efficiency as it eliminates the high number of false positives produced by dipstick testing. Strategies that use routine microscopy may be associated with high numbers of false results, but evidence was lacking regarding the accuracy of routine microscopy and estimates were adopted for the model. The model for imaging the upper urinary tract showed that US detects more tumours than IVU at one-third of the cost, and is also associated with fewer false results. For any cause of haematuria, CT was shown to have a mean incremental cost-effectiveness ratio of £9939 in comparison with the next best option, US. When US is followed up with CT for negative results with persistent haematuria, it dominates the initial use of CT alone, with a saving of £235,000 for the evaluation of 1000 patients. The model for investigation of the lower urinary tract showed that for low-risk patients the use of immediate cystoscopy could be avoided if cystoscopy were used for follow-up patients with a negative initial test using tumour markers and/or cytology, resulting in a saving of £483,000 for the evaluation of 1000 patients. The clinical and economic impact on delayed detection of both upper and lower urinary tract tumours through the use of follow-up testing should be evaluated in future studies.

Conclusions: There are insufficient data currently available to derive an evidence-based algorithm of the diagnostic pathway for haematuria. A hypothetical algorithm based on the opinion and practice of clinical experts in the review team, other published algorithms and the results of economic modelling is presented in this report. This algorithm is presented, for comparative purposes, alongside current US and UK guidelines. The ideas contained in these algorithms and the specific questions outlined should form the basis of future research. Quality assessment of the diagnostic accuracy studies included in this review highlighted several areas of deficiency.

Contents

Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

MEASURES OF DIAGNOSTIC TEST PERFORMANCE

This section summarises the measures of diagnostic test performance used in the review, and how these are calculated.

		Haematuria	
		Present	Absent
Test result	+	*a*	*b*
	–	*c*	*d*

True positives (TP)	Correct positive test result: *a* – number of diseased persons with a positive test result
True negatives (TN)	Correct negative test results: *d* – number of non-diseased persons with a negative test result
False positives (FP)	Incorrect positive test result: *b* – number of non-diseased persons with a positive test result
False negatives (FN)	Incorrect negative test result: *c* – number of diseased persons with a negative test result
Sensitivity	$a/(a + c)$ – Proportion of people with the target disorder who have a positive test result
Specificity	$d/(b + d)$ – Proportion of people without the target disorder who have a negative test result
Likelihood ratio (LR) **– positive (LR +ve)** **– negative (LR –ve)**	Describes how many times a person with disease is more likely to receive a particular test result than a person without disease. A likelihood ratio of a positive test result is usually a number greater than 1 and a likelihood ratio of a negative test result usually lies between 0 and 1 LR + $= [a/(a + c)]/[b/(b + d)]$ $=$ sensitivity/(1 – specificity) LR – $= [c/(a + c)]/[d/(b + d)]$ $=$ (1 – sensitivity)/specificity

continued

Diagnostic odds ratio (DOR)

Used as an overall (single indicator) measure of the diagnostic accuracy of a diagnostic test. It is calculated as the odds of positivity among diseased persons divided by the odds of positivity among non-diseased persons. When a test provides no diagnostic evidence then the DOR is 1.0.

DOR = $(a/c)/(b/d)$
= [sensitivity/(1 – specificity)]/[(1 – sensitivity)/specificity]
= LR+/LR– = ad/bc

Predictive value

Positive predictive value: the probability of disease among all persons with a positive test result

Positive predictive value (PPV) = $a/(a + b)$

Negative predictive value: the probability of non-disease among all persons with a negative test result

Negative predictive value (NPV) = $d(c + d)$

Predictive values depend on disease prevalence: the more common a disease is, the more likely it is that a positive test result is right and a negative result is wrong

Receiver operating curve (ROC)

A ROC represents the relationship between 'true positive fraction' (sensitivity) and 'false positive fraction' (1 – specificity). It displays the trade-offs between sensitivity and specificity as a result of varying the cut-off value for positivity in case of a continuous test result

Summary ROC curve (sROC)

The summary ROC approach models test accuracy, defined by the logarithm of the diagnostic odds ratio [D = logit(sensitivity) – logit(1 – specificity)], as a function of test threshold [S = logit(sensitivity) + logit (1 – specificity)]. S relates to the positivity threshold: it has a value of 0 in studies where sensitivity equals specificity, it is positive in studies where sensitivity is higher than specificity and negative when specificity is higher than sensitivity. For a set of primary studies, the following linear regression model is fitted:

$D = \alpha + \beta S$

where D is the log (odds ratio) in each study, α is the intercept, which is the expected log (odds ratio) when $S = 0$; β is the coefficient of S, indicating whether the log (diagnostic odds ratio) varies with the threshold.

The estimated summary ROC can be plotted by computing the expected sensitivity for each value of 1 – specificity across the range of the observed values. The expected sensitivity is given by sensitivity = $[1 + e^{-\alpha(1-\beta)}V^{(1+\beta)(1-\beta)}]^{-1}$
where V = specificity/(1 – specificity)

List of abbreviations

AUA	American Urological Association
BNF	British National Formulary
BP	blood pressure
BTA	bladder tumour antigen
CCT	controlled clinical trial
CEA	carcinoembryonic antigen
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CRD	Centre for Reviews and Dissemination
CT	computed tomography
DIM	differential interference microscopy
DOR	diagnostic odds ratio
EED	Economic Evaluation Database
FISH	fluorescent *in situ* hybridisation
FPR	false positive rate
hpf	high-power field
ICER	incremental cost-effectiveness ratio
IgA	immunoglobulin A
IVP	intravenous pylography
IVU	intravenous urography
JHIS	Japanese Health Insurance System
KUB	kidney, ureter and bladder
LR	likelihood ratio
LR–	negative likelihood ratio
LR+	positive likelihood ratio
LY	life-year
MCM5	Minichromosome Maintenance 5 Protein
MDCTU	multidetector CT urography
MRI	magnetic resonance imaging
MSU	mid-stream urine
NA	not applicable
NMP22	nuclear matrix protein 22
NPV	negative predictive value
OR	odds ratio
PCM	phase contrast microscopy
PKD	polycystic kidney disease
PPV	positive predictive value
PSA	probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life-year
RBC	red blood cell
RCT	randomised controlled trial
RDC	red blood cell volume distribution
RDOR	relative diagnostic odds ratio
ROC	receiver operating characteristic
SIGN	Scottish Intercollegiate Guidelines Network
sROC	summary receiver operating characteristic
TCC	transitional cell carcinoma
TPR	true positive rate
TPS	tissue polypeptide-specific antigen
UBCTM	urinary bladder cancer tumour marker
US	ultrasound scanning
UTI	urinary tract infection

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

The causes of haematuria can be serious (e.g. bladder cancer) or benign (e.g. vigorous exercise). Haematuria is often detected in primary care settings using urine dipstick tests and this may be regarded as the initiating step in a diagnostic chain. The second step is the establishment of the underlying cause. The possibility of a distinction between nephrological and urological causes is important to allow correct specialist referral at an early stage. The aim of management should be prompt detection and treatment of serious underlying causes of haematuria, whilst minimising the number of tests conducted in patients with benign causes.

Objectives

The objectives of this review were to:

- Summarise the evidence for the efficacy of existing diagnostic algorithms for the investigation of haematuria.
- Evaluate the efficacy of tests to detect haematuria.
- Evaluate the efficacy of tests to determine the underlying cause of haematuria.
- Determine the diagnostic accuracy of tests used to detect haematuria and to investigate its underlying causes.
- Analyse the cost-effectiveness of the detection and investigation of haematuria using a critical review of the existing cost-effectiveness literature and decision analysis.
- Develop a preliminary diagnostic algorithm for healthcare professionals.

Methods

A systematic review was undertaken according to published guidelines. Decision analytic modelling was undertaken, based on the findings of the review, expert opinion and additional information from the literature, to assess the relative cost-effectiveness of plausible alternative tests that are part of diagnostic algorithms for haematuria.

Data sources

Studies were identified through extensive searches of electronic databases, Internet searches, handsearching journals and conference proceedings, scanning reference lists of included papers and consultation with experts in the field.

Study selection

Two reviewers independently screened titles and abstracts for relevance. Full papers of potentially relevant studies were assessed for inclusion by one reviewer and checked by a second. Published and unpublished studies in any language were eligible for inclusion.

Inclusion/exclusion criteria

Separate inclusion criteria, which related to study design, participant characteristics and outcome measure, were derived for each objective.

Data extraction

Data extraction and quality assessment were performed using standardised forms. All diagnostic accuracy studies were checked by a second reviewer. The quality of the included studies was evaluated using published checklists and criteria.

Data synthesis

Diagnostic accuracy studies

Results were analysed according to test grouping (detection of haematuria, haematuria as a test for disease and further investigation of patients with haematuria) and clinical aim of studies. The sensitivity, specificity and likelihood ratios (of both positive and negative tests results) and diagnostic odds ratios were calculated. Individual study results were presented graphically in receiver operating characteristic space. Pooled estimates of positive and negative likelihood ratios were calculated and median likelihood ratios and interquartile ranges were additionally presented. Heterogeneity was investigated using the Q statistic through visual examination of study results and regression analyses.

Economic evaluations

The identified studies were described and evaluated in a narrative summary, presented in

tables and in graphical displays. Separate cost-effectiveness models were developed using the best available evidence to determine the cost-effectiveness of alternative diagnostic strategies in a UK setting.

Development of an algorithm for the investigation of haematuria

Data identified by the review were insufficient to inform the development of an evidence-based algorithm. A hypothetical algorithm based on the opinion and practice of clinical experts, combined with information derived from algorithms reported in the literature and the results of the modelling, is presented. This may serve as a guide regarding potential options for current practice and direction of future research.

Results

The searches identified over 12,000 potentially relevant studies. A total of 118 studies met the inclusion criteria (including eight economic evaluations).

Effectiveness of the investigation of haematuria

No studies that evaluated the effectiveness of diagnostic algorithms for haematuria or the effectiveness of screening for haematuria or investigating its underlying cause were identified.

Diagnostic accuracy of tests used to detect haematuria and to determine underlying causes

Detection of haematuria (19 studies)

Eighteen out 19 identified studies evaluated dipstick tests. Data from the majority suggested that these are moderately useful in establishing the presence of, but cannot be used to rule out, haematuria.

Haematuria as a test for the presence of a disease (six studies)

These studies indicated that the detection of microhaematuria cannot alone be considered a useful test either to rule in or rule out the presence of a significant underlying pathology (urinary calculi or bladder cancer).

Further investigation to establish the underlying cause of haematuria (80 studies)

Forty-eight of 80 studies addressed methods to localise the source of bleeding (renal or lower urinary tract). The methods and thresholds described in these studies varied greatly, precluding any estimate of a 'best performance' threshold that could be applied across patient groups. However, studies of red blood cell morphology that used a cut-off value of 80% dysmorphic cells for glomerular disease reported consistently high specificities (potentially useful in ruling in a renal cause for haematuria). The reported sensitivities were generally low.

Twenty-eight studies included data on the accuracy of laboratory tests (tumour markers, cytology) for the diagnosis of bladder cancer. The majority of tumour marker studies evaluated nuclear matrix protein 22 or bladder tumour antigen. The sensitivity and specificity ranges suggested that neither of these would be useful either for diagnosing bladder cancer or for ruling out patients for further investigation (cystoscopy). However, the evidence remains sparse and the diagnostic accuracy estimates varied widely between studies.

Fifteen studies evaluating urine cytology as a test for urinary tract malignancies were heterogeneous and poorly reported. The calculated specificity values were generally high, suggesting some possible utility in confirming malignancy. However, the evidence suggests that urine cytology has no application in ruling out malignancy or excluding patients from further investigation.

Fifteen studies evaluated imaging techniques [computed tomography (CT), intravenous urography (IVU) or ultrasound scanning (US)] to detect the underlying cause of haematuria. The target condition and the reference standard varied greatly between these studies. The diagnostic accuracy data for several individual studies appeared promising but meaningful comparison of the available imaging technologies was impossible.

Economic evaluations/modelling

Eight studies met the inclusion criteria. These studies addressed different parts of the diagnostic chain (e.g. screening programmes, laboratory investigations, full urological work-up). No single study addressed the complete diagnostic process. The review also highlighted a number of methodological limitations of these studies, including their lack of generalisability to the UK context. Separate decision analytic models were therefore developed to progress estimation of the optimal strategy for the diagnostic management of haematuria. The economic model for the detection of microhaematuria found that immediate microscopy following a positive dipstick

test would improve diagnostic efficiency as it eliminates the high number of false positives produced by dipstick testing. Strategies that use routine microscopy may be associated with high numbers of false results, but evidence was lacking regarding the accuracy of routine microscopy and estimates were adopted for the model. The model for imaging the upper urinary tract showed that US detects more tumours than IVU at one-third of the cost, and is also associated with fewer false results. For any cause of haematuria, CT was shown to have a mean incremental cost-effectiveness ratio of £9939 in comparison with the next best option, US. When US is followed up with CT for negative results with persistent haematuria, it dominates the initial use of CT alone, with a saving of £235,000 for the evaluation of 1000 patients. The model for investigation of the lower urinary tract showed that for low-risk patients the use of immediate cystoscopy could be avoided if cystoscopy were used for follow-up patients with a negative initial test using tumour markers and/or cytology, resulting in a saving of £483,000 for the evaluation of 1000 patients. The clinical and economic impact on delayed detection of both upper and lower urinary tract tumours through the use of follow-up testing should be evaluated in future studies.

Conclusions

There are insufficient data currently available to derive an evidence-based algorithm of the diagnostic pathway for haematuria. A hypothetical algorithm based on the opinion and practice of clinical experts in the review team, other published algorithms and the results of economic modelling is presented in this report. This algorithm is presented, for comparative purposes, alongside current US and UK guidelines. The ideas contained in these algorithms and the specific questions outlined should form the basis of future research.

Quality assessment of the diagnostic accuracy studies included in this review highlighted several areas of deficiency. Future studies should follow the STARD guidelines for reporting of diagnostic accuracy studies.

The following major outstanding questions for future research were identified:

- Is screening/testing for haematuria effective?
- Is investigation of the cause of haematuria effective?
- Which patients with asymptomatic haematuria need full investigation, and is there a subset of patients who require fewer or no further investigations?
- What is the most effective means of following those with haematuria who test negative on all initial investigations? Specifically, what repeat screening test should be done, at what frequency and for how long, and what are the indications for repeat or additional investigations?
- What is the impact of sample degradation with time on the performance of microscopy for the detection of microhaematuria?
- What would be the incremental benefit of routinely using urinary blood cell morphology techniques alongside simple renal function tests (e.g. proteinuria) in order to improve direct referral to nephrology?
- What is the clinical and economic impact of delayed detection of life-threatening causes of haematuria through the use of non-reference standard tests with follow-up screening using reference tests?

Areas where further research may be useful due to the limitations of the existing evidence base (e.g. few studies, heterogeneous results, important questions not addressed) are:

- the accuracy of dipstick tests in detecting haematuria
- factors that affect the performance of urine cytology
- diagnostic accuracy of tumour markers (accuracy of markers not yet evaluated, accuracy of tumour markers when used either in combination, or in serial in the individual)
- the cumulative diagnostic effect of conducting imaging studies.

Chapter 1
Background

What is haematuria and what are its causes?

Haematuria is defined as the presence of red blood cells (RBCs) in the urine, either visible (macroscopic haematuria) or detected by direct microscopy (microscopic haematuria).[1] Quantitation of RBCs has resulted in different cut-off values being used for the definition of microscopic or occult haematuria. Established definitions have used threshold values of ≥3 RBCs per high-power field (hpf)[2] and ≥5 RBCs/hpf.[3] A chemical dipstick method to detect blood in urine provides an instant result and is often the method of detection of microscopic haematuria in the primary care setting. The definition of dipstick haematuria is not necessarily synonymous with the quantitative definition and 'dipstick haematuria' can be considered as a diagnostic entity.

Haematuria can be broadly classified as nephrological or urological in origin. Any glomerular disease may result in microscopic haematuria. Active glomerular nephritis and acute interstitial nephritis are associated with large numbers of usually dysmorphic RBCs and RBC casts. Nephrotic syndrome and progressive glomerular nephritis typically have fewer erythrocytes on microscopy. Other causes to consider are immunoglobulin A (IgA) nephritis, thin membrane disease and hereditary nephritis or Alports disease. Urological causes include tumours [transitional cell carcinoma, renal carcinoma (Wilms tumour in children) and, infrequently, prostate cancer], urinary tract infection, stone disease and bleeding from benign prostate conditions. Less common causes include urethral caruncle, meatal ulcers, trauma, loin pain, haematuria syndrome, familial telangleectasia, arteriovenous malformation, endometriosis and factitious (added) blood. Microscopic haematuria may be detected in the absence of any underlying pathology, such as after vigorous exercise.[4]

Epidemiology

The prevalence of asymptomatic microscopic haematuria varies between 0.19 and 21%;[2,5] this range is largely accounted for by differences in age and sex in the populations studied. Screening studies have suggested that the prevalence of asymptomatic microscopic haematuria in the UK adult male population is around 2.5%.[6] This figure is thought to increase with the age of the population screened; prevalence in middle age may be similar to that of the general population,[7,8] increased (up to 22%) in males over 60 years of age.[9]

Risk groups for disease in patients with haematuria

The significance of microscopic haematuria varies. In young people, in whom malignancies of the urinary tract are relatively uncommon, the prevalence of significant underlying pathology for haematuria found at screening is low (in the range 0–7.2%).[10] Glomerular causes for haematuria predominate in this age group, and initial evaluation by a nephrologist may be more appropriate. Risk factors for significant disease include smoking history, occupational exposure to chemicals (benzenes or aromatic amines), history of gross haematuria, age over 40 years, history of urological disease, history of urinary tract infection, analgesic abuse and history of pelvic irradiation.[11] Mandatory investigation of the older patient has been advocated, as the prevalence of significant pathologies is said to increase with age.[6] Urological disease has been reported in up to 52%, with bladder tumours in up to 5% of males over 60 years old screening positive for microscopic haematuria.[9] In those from the general population who screen positive for microscopic haematuria, the prevalence of urological or nephrological disease has been estimated at 13–50% and the prevalence of malignancy at 1–2%.[6,12,13] A large contemporary UK series has been reported, in which important disease (cancer, nephrological disease, stone disease) was diagnosed in 26.4% of patients evaluated for haematuria, with an incidence of cancer of 9.4% in patients with microscopic haematuria and 24.2% in patients with macroscopic haematuria. The likelihood of detecting cancer was both gender and age related.[14]

Macroscopic haematuria is associated with a higher prevalence of serious underlying pathology; a prevalence of 22% for urological

malignancies has been reported.[13] As such, further investigation is generally considered to be mandatory.[15]

The value of urinalysis screening as a marker for the future development of malignancies remains open to debate. It has been suggested that the presence of microscopic haematuria at urinalysis screening can serve as a predictor for the development of bladder cancer.[16] However, equivalent probabilities of developing urological malignancies have also been reported in participants screening positive and negative for haematuria.[7] A screening study conducted in Japan showed an increased risk of developing end-stage renal disease associated with microscopic haematuria.[17]

Diagnostic tests for haematuria

There are two distinct phases in the investigation of haematuria: determining whether and to what degree haematuria is present, and identifying the cause.

History and physical examination

The initial clinical evaluation can provide indications as to the cause of haematuria and can help to eliminate potential benign causes (e.g. vigorous exercise, menstruation and trauma). The risk factors for significant disease (as outlined above) should also be considered.

Obtaining a urine sample

In most cases, collection of an uncontaminated mid-stream urine (MSU) sample is adequate for use in tests for haematuria.

Urinalysis

Dipstick test (reagent strip tests)

Microscopic haematuria is frequently detected using a dipstick[18] to test for 'haem' residues in the urine. This indirect method is often the initial investigation in primary and secondary care settings. The dipstick test is commonly considered to be sensitive for the detection of RBCs below the defined 3 RBCs/hpf threshold for microscopic haematuria. It has been suggested that if the result of a dipstick test is positive, then microscopy should always be undertaken.[19] This statement requires further investigation and will be tested by the second and fourth objectives of the review [see the section 'Objectives' (p. 5)]. The dipstick test will detect both filtered haemoglobin and myoglobin; not all patients with significant pathology, including cancer, will have blood in their urine at all times, and variation in the reliability of microscopy in detecting haematuria may result from differences in the technique used and delays in the sample reaching the laboratory.

Further investigation to establish the underlying cause of haematuria

Further investigation of haematuria may involve invasive procedures and, since a diagnosis of underlying cause is by no means certain, full evaluation is unlikely to be appropriate for all presenting patients. It is therefore important to establish a consistent diagnostic pathway. Guidance produced by the American Urological Association (AUA) states that: "Patients with asymptomatic microscopic haematuria who are at risk for urological disease or primary renal disease should undergo an appropriate evaluation. In patients at low risk for disease, some components of the evaluation may be deferred."[20] In patients with risk factors for disease but negative initial investigations, follow-up may be warranted with repeat investigations performed following an appropriate interval.

Urinalysis

Microscopy

In addition to quantitation of RBCs/hpf, microscopic evaluation is a means to detect the presence of dysmorphic RBCs and red cell casts; these give an indication that bleeding may be glomerular in origin.[11] Accurate determination of RBC morphology may require inverted phase contrast microscopy.[19] Automated systems of urinalysis may provide an alternative approach for distinguishing between glomerular and non-glomerular haematuria.[21]

Culture

Asymptomatic haematuria may occur as a result of asymptomatic urinary tract infection.[22] Culture can be used to rule out infection, and it has been suggested that if white cells are present in the urine, then culture should be mandatory.[19]

Cytology

Cytological evaluation of exfoliated cells in the voided urine can be used to detect urothelial cancers. The sensitivity of this procedure may depend upon a variety of factors, including the grade of the tumour and the expertise of the cytopathologist.[11] False-positive findings can be observed, particularly among patients with urinary

calculi and chronic infection and inflammation, and those who have received radiotherapy or chemotherapy.[22]

Voided markers

A variety of voided urinary markers have been evaluated in the detection of bladder and urinary tract cancers, most commonly bladder tumour antigen (BTA)[23–25] and nuclear matrix protein 22 (NMP22).[26–29] Recent AUA guidelines have stated that the available data are insufficient to recommend the routine use of voided urinary markers in the evaluation of patients with microscopic haematuria.[11] Current evidence is summarised in the section 'Tumour markers' (p. 60).

Routine biochemistry

An elevated serum creatinine can be an indication of a nephrological cause of haematuria. Proteinuria, elevated creatinine and/or hypertension may indicate renal disease and these patients require a nephrological assessment.

Cystoscopy

Cystoscopy is an invasive procedure that permits the visualisation of the urethra, urinary bladder and ureteral orifices and has been described as the gold standard for clinically detectable lesions of the lower urinary tract.[22] The procedure can be carried out using either a rigid or flexible cystoscope, although flexible cystoscopy is less traumatic.[19] Cystoscopy carries a risk of urinary infection of about 5%.[30]

Imaging

Abdominal radiology

A plain radiograph of the abdomen or KUB (kidney, ureter and bladder) may be useful in evaluating younger patients when the most common explanation for microscopic haematuria is a renal calculus. However, around 15% of renal calculi are not radiopaque, and the presence of phleboliths may cause false-positive results.[22]

Intravenous urography (IVU)/intravenous pylography (IVP)

This has traditionally been the gold standard investigation method for the detection of upper urinary tract lesions.[31] IVU by itself has limited sensitivity in detecting small renal masses and ultrasound scanning (US) may be needed for further lesion characterisation.[11] IVU requires the injection of a contrast medium to provide a precise anatomical image of the KUB and this carries a risk of allergic reactions in about 1 in 10,000 cases, which may be serious in about 1 in 100,000, even with the new non-ionic contrast media.

Ultrasound

Some authors have discussed abdominal ultrasonography as an alternative to IVU,[32] whereas others have suggested that both IVU and US are necessary for the evaluation of microscopic haematuria in low- and high-risk groups.[14] A criticism of ultrasonography has been that its usefulness may depend a great deal upon the skill or experience of the operator.[19]

Computed tomography (CT)

Like US, CT has been recommended as a technique for the characterisation of lesions detected by IVU.[11] In particular, the technique has been considered useful in the evaluation of suspected urinary stones.[33] Coronal reformatted images provide an image similar to IVU and may facilitate stone and tumour localisation.[33]

Magnetic resonance imaging (MRI)

MRI is more expensive and less widely available than the other modalities, and so is rarely used in the evaluation of haematuria. It may occasionally be considered as a problem-solving approach for patients who require additional imaging after CT or US.[11]

Nephrological tests and renal biopsy

Immunological investigations and renal biopsy may be indicated when there is evidence of parenchymal disease such as elevated plasma creatinine, significant proteinuria or raised blood pressure. Specific therapeutic interventions may be available if a diagnosis of immune-mediated renal disease is established.

Chapter 2

Research questions

Aim of the project

The aim of the project was to determine the most effective diagnostic strategy for the investigation of microscopic and macroscopic haematuria in adults.

Objectives

The objectives were as follows:

- To summarise the evidence for the efficacy of existing diagnostic algorithms for the investigation of haematuria.
- To evaluate the efficacy of tests used to detect haematuria, both in population screening and in the work-up of symptomatic patients.
- To evaluate the efficacy of further investigation to determine the underlying cause of confirmed haematuria.
- To determine the diagnostic accuracy of tests used to detect haematuria and to investigate its underlying causes.
- To analyse the cost-effectiveness of the detection and investigation of haematuria using critical review of the existing cost-effectiveness literature, and decision analytic modelling to develop estimates of the cost-effectiveness of alternative diagnostic strategies.
- To develop a preliminary diagnostic algorithm for healthcare professionals who manage patients with haematuria, which could be evaluated in future primary research.

Chapter 3

Review methods

An advisory panel (Appendix 1) was established. In addition to providing subject-specific input during the review, members of the panel were invited to offer comment on the protocol and draft report. The systematic review was undertaken in accordance with the Centre for Reviews and Dissemination (CRD) guidelines for undertaking systematic reviews and published guidelines on the meta-analysis of diagnostic tests.[34–36]

Search strategy

A database of published and unpublished literature was assembled from systematic searches of electronic sources, handsearching and consultation with experts in the field.

Studies were identified by searching major medical databases such as MEDLINE, EMBASE, BIOSIS, Pascal, Science Citation Index and LILACS from inception to October 2003. Update searches were undertaken in August 2004 (see Appendix 2 for detailed search strategies).

In addition, information on studies in progress, unpublished research or research reported in the grey literature was sought by searching a range of relevant databases including the following: National Research Register, Systems for Information in Grey Literature (SIGLE), Dissertation Abstracts, the metaRegister of Controlled Trials, National Technical Information Service and GrayLit network. Five key journals (*Urology*, *The Journal of Urology*, *BJU International*, *Nephron* and *Deutsche Medizinische Wochenschrift*) were handsearched from 2000 to present including available early online publications. The most recent issues and any available forthcoming papers in the *American Journal of Clinical Pathology*, *Clinical Nephrology*, *British Journal of Radiology*, *Lancet*, *JAMA* and *BMJ* were searched to complement the electronic searches. The search incorporated regular issues and supplements. The proceedings of 11 relevant conferences from 2000 to date were searched to find further unpublished studies.

Internet searches to identify studies were carried out using OMNI (www.omni.ac.uk/) and Google (www.google.co.uk/).

Attempts to identify further studies were made by contacting clinical experts and examining the reference lists of all retrieved articles.

Searches for economic evaluations were undertaken on the NHS Economic Evaluation Database (NHS EED) and the Health Economic Evaluation Database, alongside searches for economic working papers in the Economics Working Paper Archive. The literature database assembled for the other sections of the review was also scanned for economic evaluations. Additional searches were carried out for economic models for bladder cancer and quality of life for superficial bladder cancer in MEDLINE and EMBASE. Detailed search strategies are reported in Appendix 2.

Inclusion/exclusion criteria

Two reviewers screened titles and abstracts for relevance independently and any disagreements were resolved by consensus. Full papers of potentially relevant studies were obtained and assessed for inclusion by one reviewer and checked by a second. There were separate inclusion criteria for each objective addressed by the systematic review component of the project, as follows.

Evaluation of the efficacy of diagnostic algorithms for the investigation of haematuria

Studies of any design that evaluated the effectiveness of diagnostic algorithms by comparison of alternative strategies were eligible for inclusion; no studies of this type were identified. Publications reporting diagnostic algorithms without evaluation are listed in Appendix 6.

Effectiveness screening for haematuria

Randomised controlled trials (RCTs) of the efficacy of screening programmes, reporting patient outcomes, were eligible for inclusion.

Effectiveness of further investigations to determine the underlying cause of haematuria

RCTs or non-randomised controlled clinical trials (CCTs) of diagnostic tests that investigated patient outcomes were eligible for inclusion.

Evaluation of the diagnostic accuracy of tests used to detect haematuria and to determine its underlying causes

Diagnostic cohort or case–control studies evaluating any test or combination of tests used in the detection or investigation of haematuria were eligible for inclusion. Studies were excluded if no reference standard was reported, if insufficient information was reported to allow construction of a 2×2 table, if included patients were all paediatric (<18 years old) or if there were <20 participants. Studies of tests used to investigate the underlying cause of haematuria were be excluded if they included a mixed population of patients from which 2×2 data could not be separately extracted for the subset of patients with haematuria.

Economic evaluations

Studies were included as economic evaluations if they met the criteria of being full economic evaluations, namely that they included an explicit analysis of both costs and effects for an intervention and at least one comparator[37] and were considered to be useful in answering the research questions relating to cost-effectiveness.

Data extraction

Data extraction forms for diagnostic accuracy studies were developed using Microsoft Access. These were piloted on a small selection of studies. No trials evaluating the efficacy of diagnostic algorithms, testing for haematuria or investigation of the cause of haematuria were identified. Data extraction was performed by one reviewer and checked by a second. Foreign language papers were extracted by one reviewer, accompanied by a speaker of that language, and the data were entered directly into the Access database. Data extraction of non-English language studies was not checked by a second reviewer. The following information was extracted for all studies: bibliographic details; objective; country and location (primary/secondary care) where the study was conducted; study design; number of participants; participant characteristics (age, sex, presentation); details of the index test(s) investigated (including definition of a positive test); details of the reference standard of diagnosis (including definition of a positive test); reported values for sensitivity and specificity; results (2×2 data); time elapsed between the index test and reference standard; details of any subgroup analyses, adverse events or drop-outs reported. Economic studies identified by the systematic review are discussed in Chapter 7.

Quality assessment

Quality assessment forms were developed using Microsoft Access for the different study designs included in the review. Quality assessment was carried out by one reviewer and checked by a second.

Diagnostic accuracy studies

Included diagnostic accuracy studies (for both diagnosis and further investigation of haematuria) were assessed for methodological quality using the QUADAS tool.[38,39] The 14 items of the QUADAS tool check the appropriateness of the patient spectrum composition, whether selection criteria for patients have been described, the appropriateness of the reference standard, whether disease progression bias has been avoided (whether the time lapsed between index test and reference standard was sufficiently short to make a change in disease status unlikely), whether partial and/or differential verification bias have been avoided (all participants received verification using the same reference standard of diagnosis) and whether incorporation bias (independence of index test and reference standard) has been avoided. The checklist also addresses the question of whether the execution of the reference standard and index tests has been reported in sufficient detail to permit replication and whether test review bias, diagnostic review bias and clinical review bias have been avoided (the results of tests have been interpreted independently of each other and with appropriate clinical information available). Finally, the studies were checked with regard to the reporting of uninterpretable results and whether all withdrawals had been accounted for. The QUADAS tool together with details on how studies were scored is provided in Appendix 3.

RCTs/CCTs

No studies of this type were identified.

Economic evaluations

Quality assessment of each study was undertaken using two approaches. First, for each study a critical (textual) summary was completed in accordance with the approach adopted by the NHS EED.[37] This includes an appraisal of the validity of choice of comparator/s, the validity of the analysis of effectiveness results, the validity of the benefit measure used in the economic analysis, the validity of the cost results, other issues, including whether or not the authors compared their results with those of other (similar) studies, whether generalisability was addressed by the authors and the principal limitations and

strengths of the study, and finally the implications of the study in terms of clinical practice and future research.

Second, the quality of economic evaluations was assessed using a modified version of the 35-point checklist developed for authors of economic submissions to the *BMJ*,[40,41] to which an additional item was added (item 36) in order to report whether or not the authors had addressed the issue of the generalisability of the results. Each item in the checklist was given one of four responses (score given in parentheses): (a) Yes (1), (b) No (0), (c) Not Applicable (NA) (not counted) and (d) Partial (0.5). In order to provide an overview of the quality of each study, a percentage of applicable items that were answered 'Yes' was provided, calculated as total [('yes'/(36 – NA) × 100)].[42]

Although not directly related to an assessment of study quality, a summary of the direction of the results of economic evaluations included in the review, in terms of costs and effects, was provided using the hierarchical permutation matrix.[43] The checklist and matrix assessments were reported in a single table for clarity and ease of interpretation.

Statistical analysis

Diagnosis/further investigation of haematuria

Results were analysed according to test grouping: Within these groups, tests were examined according to the specific tests or test combinations reported in the literature. Combinations of tests were analysed as test combinations, where appropriate.

For each test, the ranges of sensitivity, specificity and likelihood ratios (LRs) (of both positive and negative tests results), and diagnostic odds ratios (DORs) were calculated. These were presented in tables. To account for 0 cells in the 2 × 2 tables when calculating pooled estimates, 0.5 was added to every cell for all 2 × 2 tables as recommended by Moses and colleagues.[44] Individual studies results were presented graphically using summary receiver operating characteristic (sROC) curves. These were estimated using the following equation:

$$Sen = \frac{1}{1 + \frac{1}{e^{\frac{\alpha}{1-\beta}} \times \left(\frac{1 - Spe}{Spe}\right)^{\frac{1+\beta}{1-\beta}}}}$$

where *Sen* = sensitivity and *Spe* specificity. The parameters α and β were calculated using the following regression equation:

$$D = \alpha + \beta S$$
$$D = [\text{logit(TPR)} - \text{logit(FPR)}] = \log(\text{DOR})$$
$$S = [\text{logit(TPR)} + \text{logit(FPR)}]$$

$$\text{logit(TPR)} = \ln[\text{TPR}/(1 - \text{TPR})]$$
$$\text{logit(FPR)} = \ln[\text{FPR}/(1 - \text{FPR})]$$

This was estimated by regressing *D* against *S*, weighting according to sample size, for each study. Beta provides an estimate of the extent to which *D* is dependent on the threshold used. If $\beta = 0$ (when the line is symmetric with respect to the line TPR = 1 – FPR), or not significantly different from 0, then the DOR is not affected by the threshold used. When this was the case, the DOR was pooled according to standard methods for pooling odds ratios (ORs).[45] In such cases, the following equation was used to calculate the sROC curves:

$$Sen = \frac{1}{1 + \frac{1}{\text{DOR}_T \times \left(\frac{1 - Spe}{Spe}\right)}}$$

LRs were selected as the measure of test performance for further analysis as physicians more easily interpret these measures than sensitivity and specificity. Heterogeneity of LRs was investigated using the *Q* statistic[46] and through visual examination of Forest plots of study results.[47] Pooled estimates of positive and negative LRs (LR+ and LR–) were calculated where possible. However, owing to the significant heterogeneity present in most tests, median LRs, together with their interquartile ranges, were also calculated and presented.

Where sufficient data were available, heterogeneity was further investigated using regression analysis. The sROC model,[44] as outlined above, was extended to include the covariates presented below.[48] A multivariate linear regression analysis was conducted, again weighted by sample size. QUADAS items were investigated as possible sources of heterogeneity. Studies were generally poorly reported, resulting in insufficient data to investigate any further potential sources of heterogeneity.

Initially, univariate analysis was performed with items included individually in the model. Items

which showed a significant association at the 10% significance level with *D* were investigated further using stepwise multivariate models. In this approach, all items found to be significant in the univariate models were entered into the multivariate model and then dropped in a stepwise fashion with the least significant item dropped first. The final model was achieved when all items remaining in the model showed a significant association with *D* at the 5% level.

Economic evaluations

Statistical analysis for economic evaluations was relevant only in terms of reporting the results of statistical tests that were provided in economic evaluations included in the review. For the report's modelling studies of diagnostic strategies in detecting haematuria and its underlying causes, probabilistic sensitivity analyses were conducted to explore uncertainty in the input parameters used to populate the models. Modelling methods are described in detail in Chapter 7.

Algorithm development

The data obtained from studies meeting the inclusion criteria for the first four objectives of the review [see the section 'Objectives' (p. 5)] were insufficient to facilitate the development of any evidence-based algorithm. The algorithm presented in Appendix 12 was generated taking into account the content of existing algorithms (not evaluated in comparative studies and therefore not eligible for inclusion under the first objective), the opinion of clinical experts on the project team and the results of the economic modelling exercise. As such, this algorithm should be treated as a hypothetical proposition, which may be used to guide future research rather than as an evidence-based clinical guideline.

Chapter 4

Details of studies included in the review

Diagnosis of haematuria

Nineteen studies provided data on tests to determine the presence of haematuria (*Table 1*). With the exception of one study that compared different microscopy techniques, all studies evaluated dipstick tests.

Haematuria as a test for the presence of disease

Six studies provided data on the presence of haematuria as a test for the presence of a disease (*Table 2*).

Further investigation to determine the underlying cause of haematuria

Eighty studies provided data on further investigations to determine the underlying cause of haematuria. These are categorised according to their clinical objective:

Of these, 48 studies provided data on tests to localise bleeding to a glomerular or non-glomerular source (*Table 3*).

Thirty-two studies that were eligible for inclusion in the review evaluated tests to determine the underlying cause of haematuria (*Table 4*).

Economic evaluations

Six published studies met the inclusion criteria and these are summarised in Chapter 7. Detailed data extraction, in the form of NHS EED abstracts, is provided in Appendix 8. In addition, two abstracts containing relevant data were identified and are summarised in Chapter 7.

TABLE 1 *Studies evaluating tests to determine the presence of haematuria*

Study details	Test grouping
Arm (1986)[49]	Dipstick (N-Multistix-SG)
Bonard (1986)[50]	Dipstick (N-Multistix)
Braun (1975)[51]	Dipstick (Sangur-Test)
Demol (1980)[52]	Dipstick (Bili-Labstix)
Froom (1987)[53]	Microscopy (HPF)
Gibson (1986)[54]	Dipstick (Multistix)
Gleeson (1993)[55]	Dipstick (B.M. test)
Grinstead (1987)[56]	Dipstick (Clinitek 200/Multistix 9)
Gruhn (1974)[57]	Dipstick (N-Labstix)
Holland (1995)[58]	Dipstick [Multistix-10 (read visually; read by photometry); Combur-10 (read visually)]
Jaffe (1979)[59]	Dipstick (Multistix)
Kutter (1980)[60]	Dipstick (Combur-8)
Kutter (1974)[61]	Dipstick (Sangur-Test)
McGlone (1990)[62]	Dipstick (Ames SG10)
Messing (1987)[63]	Dipstick
Ooi (1998)[64]	Dipstick (Combur 9)
Shaw (1985)[65]	Dipstick (Multistix); (Chemstrip 9)
Wawroschek (1998)[66]	Dipstick (Combur 9)
Yoo (1995)[67]	Dipstick (Uriflet)

TABLE 2 *Studies evaluating haematuria as a test for the presence of disease*

Study details	Haematuria definition	Diagnosis and reference standard
Bove (1999)[68]	>1 RBC/hpf or positive dipstick, any RBCs, >1 RBC/hpf, >5 RBCs/hfp, >1 RBC/hpf or positive dipstick	Presence of utererolithiasis Unenhanced helical CT
Freeland (1987)[69]	Dipstick haematuria (non-haemolysed trace to 3+)	Urinary calculi present IVU and visual examination of urine
Ooi (1998)[64]	>5 RBCs/hpf for males, >10 RBCs/hpf for females; dipstick haematuria (≥ 1 RBC)	Urinary calculi present KUB and IVU, or calculi passed
Parekattil (2003)[70]	Presence of haematuria	Presence of bladder tumour Cystoscopy
Safriel (2003)[71]	≥ 2 RBCs/hpf (on 2 occasions)	Urinary calculi present CT
Sanchez Carbayo (2000)[72]	Presence of macrohaematuria; presence of microhaematuria	Presence of bladder tumour Cystoscopy

TABLE 3 *Studies evaluating tests to localise the bleeding to a glomerular or non-glomerular source*

Study details	Index test
Ahmad (1993)[73]	Microscopy (phase contrast microscopy, urinary RBC morphology)
Andreev (1995)[74]	Microscopy (phase contrast microscopy, urinary RBC morphology)
Apeland (2001)[75]	Microscopy (bright-field microscopy, using Sternheimer–Malbin stain); Autoanalyser (flow cytometry) (urinary RBC size)
Apeland (1995)[76]	Autoanalyser (flow cytometry) (urinary RBC volume and density)
Banks (1989)[77]	Autoanalyser (Coulter Counter) (urinary RBC volume)
Birch (1983)[78]	Microscopy (phase contrast microscopy, urinary RBC morphology)
de Caestecker (1992)[79]	Autoanalyser (Coulter Counter) (urinary RBC volume)
Catala Lopez (2002)[80]	Microscopy (phase contrast microscopy, acanthocyte count; phase contrast microscopy, urinary RBC morphology)
Chu (1990)[81]	Microscopy (phase contrast microscopy; differential interference microscopy; Wright's stain used)
Costa (1996)[82]	Microscopy
de Kermerchou (1993)[83]	Microscopy (phase contrast microscopy)
de Metz (1991)[84]	Microscopy (phase contrast microscopy; light microscopy) (May–Grunwald–Giemsa stain)
De Santo (1987)[85]	Microscopy (phase contrast microscopy, urinary RBC morphology)
Docci (1990)[86]	Autoanalyser (Coulter Counter) (urinary RBC size)
Docci (1988)[87]	Autoanalyser (Coulter Counter) (urinary RBC size)
Eardley (2004)[88]	Other (microalbuminuria)
Fairley (1982)[89]	Microscopy (phase contrast microscopy)
Fassett (1982)[90]	Microscopy (phase contrast microscopy)
Fünfstück (1989)[91]	Microscopy (erythrocyte morphology, urine sediment analysis)
Fukuzaki (1996)[92]	Microscopy (phase contrast microscopy; immunocytochemical staining)
Game (2003)[93]	Microscopy (phase contrast microscopy), autoanalyser (flow cytometry) (urinary RBC volume)
Gerc (1997)[94]	Microscopy (phase contrast microscopy)
Gimbel (1988)[95]	Microscopy (urinary RBC size)
Goncalves (1986)[96]	Microscopy (phase contrast microscopy)
Hirakawa (1994)[97]	Microscopy (confocal reflecting-laser microscopy)
Hirakawa (1995)[98]	Microscopy (confocal reflecting-laser microscopy)
Hyodo (1997)[99]	Autoanalyser (flow cytometry) (urinary RBC volume)
Hyodo (1999)[100]	Autoanalyser (flow cytometry) (urinary RBC volume)
Hyodo (1995)[101]	Microscopy (laser microscopy, Hyodo–Iino–Miyagawa method)
Janssens (1992)[102]	Microscopy (urinary RBC morphology); microscopy (immunocytochemical staining)
Jean (1993)[103]	Autoanalyser (Coulter Counter) (urinary RBC volume)
Kohler (1991)[104]	Microscopy (phase contrast microscopy, urinary RBC morphology)
Kore (1999)[21]	Autoanalyser (flow cytometry) (urinary RBC volume)

continued

TABLE 3 *Studies evaluating tests to localise the bleeding to a glomerular or non-glomerular source (cont'd)*

Study details	Index test
Lui (1986)[105]	Microscopy (phase contrast microscopy; benzidine dye used)
Mohammad (1993)[106]	Microscopy (phase contrast microscopy)
Nagy (1985)[107]	Microscopy (urinary RBC morphology)
Naicker (1992)[108]	Microscopy (phase contrast microscopy, urinary RBC morphology); autoanalyser (Coulter Counter) (urinary RBC volume)
Obronieka (1998)[109]	Microscopy (phase contrast microscopy)
Rath (1991)[110]	Microscopy (bright-field microscopy)
Roth (1991)[111]	Microscopy (phase contrast microscopy)
Saito (1999)[112]	Microscopy (urinary RBC morphology)
Sayer (1990)[113]	Autoanalyser (Coulter Counter) (urinary RBC volume)
Shichiri (1988)[114]	Autoanalyser (Coulter Counter) (urinary RBC size)
Singbal (1996)[115]	Microscopy (phase contrast microscopy; light microscopy (using Wright's stain); light microscopy)
Tomita (1992)[116]	Microscopy (differential interference microscopy)
Uhl (1995)[117]	Microscopy
Wankowicz (1991)[118]	Microscopy (phase contrast microscopy)
Wann (1986)[119]	Microscopy (phase contrast microscopy, urinary RBC morphology)

TABLE 4 *Studies of techniques for investigating the underlying cause of haematuria*

Study details	Index test
Akaza (1997)[29]	Tumour marker (NMP22), cytology (urine cytology)
Aslaksen (1990)[120]	Imaging (ultrasound)
Chahal (2001)[121]	Cytology
Chisholm (1988)[122]	Imaging (IVU), imaging (DMSA scintigraphy)
Chong (1999)[123]	Tumour marker (BTA), cytology
Cronan (1982)[124]	Imaging (cystosonography)
Glashan (1980)[125]	Tumour marker (urine CEA, plasma CEA)
Gray Sears (2002)[126]	Imaging (CT, IVU)
Jung (2002)[127]	cytology (urine cytology), tumour marker (UBCTM)
Kim (2002)[128]	Imaging (virtual cystoscopy)
Kirollos (1997)[129]	Tumour marker (BTA), cytology (urine cytology)
Lang (2003)[130]	Imaging (CT)
Lang (2002)[131]	Imaging (CT)
Misra (2000)[132]	Cytology (urine cytology)
Mitty (1974)[133]	Imaging (angiography)
Miyanaga (1999)[134]	Cytology (urine cytology), tumour marker (NMP22)
Miyoshi (2001)[135]	Cytology (urine cytology); tumour marker (NMP22)
Mondal (1992)[136]	Cytology (urine cytology)
Murakami (1990)[137]	Imaging (IVU), other (cystoscopy), cytology (urine cytology), imaging (US)
Oge (2001)[138]	Tumour marker (NMP22)
O'Malley (2003)[139]	Imaging (IVU; CT)
Paoluzzi (1999)[140]	Cytology (urine cytology), tumour marker (NMP22)
Quek (2002)[141]	Tumour marker (BTA), cytology (urine cytology)
Sanchez-Carbayo (2000)[142]	Tumour marker (TPS; TPS/creatinine ratio)
Sarosdy (2004)[143]	Cytology (urine cytology), tumour marker (FISH)
Speelman (1996)[144]	Imaging (ultrasound; IVU; ultrasound and IVU)
Spencer (1990)[145]	Imaging (ultrasound)
Steurer (1990)[146]	Imaging (ultrasound)
Sultana (1996)[147]	Cytology (urine cytology)
Thomas (1996)[148]	Tumour marker (BTA), cytology (urine cytology)
Yip (1996)[149]	Imaging (IVU, ultrasound)
Yip (1999)[150]	Imaging (IVU, ultrasound)

BTA, bladder tumour antigen; CEA, carcinoembryonic antigen; DMSA, dimercaptosuccinic acid; FISH, fluorescent *in situ* hybridisation; TPS, tissue polypeptide-specific antigen; UBCTM, urinary bladder cancer tumour marker.

Chapter 5

Details of studies excluded from the review

A total of 1113 of the 1242 articles ordered and screened did not meet the inclusion criteria for the review. These were excluded for the following reasons and are listed in *Table 5*:

1. Duplicate publication of an included article.
2. Report of an algorithm for the investigation of haematuria, which did not include comparative evaluation of the algorithm. These articles are listed in full in Appendix 6.
3. Economic study, which did not meet inclusion criteria for other sections of the review. These articles are evaluated in the economics section of the report.
4. Not a primary study meeting inclusion criteria for study design and evaluating tests for haematuria or to establish underlying cause in patients with haematuria.
5. Study that included only paediatric patients (<18 years old).
6. Study that included <20 participants.
7. Diagnostic accuracy study that did not report sufficient data to allow construction of a 2 × 2 contingency table.

TABLE 5 *Studies excluded from the review and reasons for exclusion*

Abbou (1982)[151] **2**
Abdurrahman (1985)[197] **5**
Abid (2001)[154] **4**
Aboim (2000)[157] **4**
Abuelo (1983)[160] **2**
Agarwal (1994)[163] **2**
Ahmed (1997)[166] **4**
Ahn (1998)[169] **4**
Akagashi (2001)[172] **7**
Albani (2004)[175] **7**
Alexopoulos (2001)[177] **4**
Alishahi (2000)[180] **4**
Alishahi (2002)[183] **4**
Allan (2000)[186] **4**
Allendorff (1996)[189] **2**
Amar (1984)[192] **7**
Amirfallah (1968)[195] **4**
Amling (2001)[198] **4**
Anders (2001)[201] **4**
Anderson (1992)[203] **4**
Andersson (1967)[205] **4**
Angulo (1999)[207] **7**
Angulo (2003)[209] **7**
Anonymous (1975)[212] **4**
Anonymous (1975)[1104] **4**
Anonymous (1989)[218] **4**
Anonymous (1989)[1142] **4**
Anonymous (1990)[220] **3**
Anonymous (1995)[223] **4**
Anonymous (1998)[226] **4**
Antolak (1969)[229] **4**
Apeland (2000)[235] **7**
Argalia (1994)[238] **4**
Arger (1972)[241] **4**
Arm (1986)[244] **4**
Arnholdt (1968)[247] **2**
Aroor (1989)[502] **4**
Asberg (1984)[250] **4**
Aslaksen (1990)[253] **4**
Aslaksen (1992)[255] **4**
Aso (1984)[258] **4**
Assa (1977)[261] **4**
Atsu (2001)[264] **4**
Atsu (2002)[267] **4**
Auwardt (1999)[270] **4**
Avidor (2000)[273] **4**
Avner (1994)[276] **4**
Avner (1995)[232] **2**
Azuma (1987)[279] **4**
Babjuk (1988)[282] **4**
Babjuk (1988)[285] **4**
Bachmann (1974)[288] **4**
Backman (1983)[291] **4**
Backman (1983)[294] **4**
Badalament (1990)[297] **4**
Bader (2000)[300] **4**
Bagley (1987)[303] **4**
Bagley (1990)[306] **4**
Bailey (1990)[309] **4**
Bailey (1996)[312] **5**
Bank (1987)[315] **7**
Banks (1989)[318] **4**
Bard (1988)[321] **4**
Barkin (1983)[324] **4**
Bartlow (1990)[330] **4**
Bateman (1991)[333] **4**
Bauer (1980)[336] **4**
Bauer (1990)[339] **4**
Baum (2003)[342] **4**
Bdesha (1993)[345] **4**
Bee (1979)[348] **4**
Belani (2003)[351] **4**
Benejam (1985)[354] **4**
Bennani (1995)[357] **4**
Bennett (1974)[360] **4**
Benson (1981)[970] **2**
Bent (2002)[363] **4**
Berger (1990)[366] **4**
Bergqvist (1981)[372] **1**
Bergqvist (2001)[375] **4**
Bergstrand (1970)[378] **4**
Bernhardt (2003)[381] **4**
Berning (1966)[383] **4**
Beroniade (1972)[386] **4**
Bhandari (2000)[389] **4**
Bhargava (1997)[392] **4**
Bhuiyan (2003)[395] **4**
Bigongiari (2000)[398] **4**
Birch (1979)[401] **4**
Birch (1980)[394] **4**
Blöchlinger (1996)[407] **2**
Bloncourt (1989)[410] **4**
Bloom (1988)[413] **2**
Blumberg (1987)[416] **7**
Blumenthal (1988)[419] **4**
Bodeker (1985)[422] **4**
Bogetic (1988)[168] **4**
Boman (2001)[425] **4**
Boman (2001)[428] **4**
Boman (2002)[431] **4**
Boman (2002)[434] **7**
Bonard (1986)[436] **1**
Bonfante (1996)[439] **4**
Bonnardeaux (1994)[442] **6**
Bono (1997)[445] **4**
Bonomo (1991)[448] **4**
Bonucchi (1995)[450] **4**
Bonucchi (1996)[453] **4**
Borisov (1982)[456] **2**
Bosniak (1990)[459] **4**
Bosompem (1996)[462] **4**

continued

TABLE 5 *Studies excluded from the review and reasons for exclusion (cont'd)*

Bottini (1990)[465] **7**
Bowen (1994)[468] **4**
Boyd (1977)[471] **4**
Boyd (1996)[474] **4**
Braedel (1973)[477] **4**
Brass (1978)[480] **4**
Brausi (2000)[483] **4**
Brehmer (2002)[486] **4**
Britton (1989)[9] **4**
Britton (1990)[491] **4**
Britton (1990)[494] **4**
Britton (1992)[497] **4**
Britton (1993)[500] **4**
Brodehl (1977)[503] **2**
Brodwall (1971)[506] **4**
Broennestam (1980)[509] **4**
Brosman (1973)[512] **4**
Brouhard (1998)[515] **4**
Brown (1987)[518] **4**
Brown (2002)[521] **4**
Brown (2002)[524] **4**
Brunet (1995)[530] **4**
Brunner (1972)[533] **4**
Bruyninckx (2003)[536] **4**
Bryden (1995)[539] **4**
Buchberger (1993)[542] **4**
Bullock (1986)[544] **4**
Buntinx (1997)[547] **4**
Burbridge (1991)[550] **4**
Burke (2002)[553] **4**
Burkholder (1969)[556] **4**
Burki (1986)[559] **4**
Burstein (1991)[562] **4**
Burtsev (1997)[565] **4**
Buzza (2001)[568] **4**
Cadoff (1992)[571] **4**
Caldas (1990)[574] **4**
Camey (1976)[577] **4**
Candela (1998)[580] **4**
Cannon (2000)[583] **4**
Cantagrel (1991)[586] **4**
Cappellini (1982)[589] **4**
Carel (1987)[595] **4**
Cariou (1997)[598] **4**
Carlson (1979)[601] **4**
Carpinito (1998)[604] **4**
Carpio (1999)[607] **4**
Carringer (1999)[610] **4**
Carroll (1984)[613] **4**
Casella (2004)[616] **4**
Cass (1973)[619] **4**
Cass (1987)[622] **4**
Catilina (1995)[625] **4**
Cattell (1990)[628] **4**
Cattell (1994)[631] **4**
Cespedes (1995)[634] **4**
Chahal (2001)[26] **4**
Chai (2001)[639] **4**
Chan (2003)[642] **4**
Chandhoke (1988)[645] **4**
Chang (1984)[648] **7**
Charvat (1968)[651] **4**
Chen (1974)[654] **4**
Chen (1995)[657] **4**
Chen (2002)[660] **2**
Choi (1990)[663] **4**
Chow (2001)[666] **4**
Christoffersen (1981)[669] **4**
Cimniak (1994)[672] **4**
Ciplea (1967)[674] **4**
Clark (1972)[677] **4**
Clarke (1990)[680] **4**
Clarkson (1996)[683] **2**
Cockett (1975)[686] **4**
Cohen (1974)[689] **4**
Cohen (1991)[692] **4**
Cohen (2003)[695] **2**
Collie (1994)[698] **4**
Connelly (1999)[22] **4**
Conzelmann (1988)[703] **7**
Copley (1986)[706] **2**
Copley (1987)[708] **4**
Corrie (1987)[711] **4**
Corrigan (2000)[714] **4**
Corwin (1988)[32] **2**
Corwin (1988)[719] **4**
Corwin (1989)[722] **4**
Coulange (1997)[725] **4**
Court Brown (1979)[728] **4**
Covarelli (2002)[731] **4**
Cronin (1989)[734] **4**
Cuellar-Cabrera (1985)[737] **4**
Culclasure (1994)[740] **4**
Cullen (1967)[743] **4**
Cutler (1990)[746] **4**
Cuttino (1985)[749] **4**
Cuttino (1987)[752] **4**
da Silva (1999)[755] **4**
Daae (1983)[758] **4**
Dales (1978)[761] **4**
Dana (1980)[764] **4**
Dana (1981)[766] **4**
Daniel (1998)[769] **4**
Dantas (1985)[772] **5**
Date (1998)[775] **6**
Datta (1982)[778] **4**
Datta (2002)[781] **7**
Daum (1988)[784] **4**
Davies (1973)[787] **4**
Davies (1999)[790] **4**
De Aledo Linos (1999)[161] **4**
De Caestecker (1988)[805] **7**
De Caestecker (1989)[808] **7**
De Caestecker (1989)[793] **7**
De Caestecker (1990)[796] **4**
de Lacey (1988)[799] **4**
de Vet (2001)[802] **4**
Dedi (2001)[811] **4**
Defelippo (1984)[814] **4**
Defidio (2001)[817] **4**
Deindoerfer (1985)[823] **4**
Del Mar (2000)[832] **4**
Delaney (1985)[826] **4**
Delanghe (2000)[829] **4**
Delomez (2002)[835] **4**
Delvecchio (2002)[1018] **4**
Demetriades (1985)[838] **4**
Demetriou (2000)[841] **4**
Dernehl (1975)[844] **4**
Desrentes (1990)[847] **4**
DeVere (1992)[850] **4**
Dhib (1991)[853] **2**
Di Natale (1999)[222] **4**
di Paolo (1993)[856] **4**
Diadyk (1991)[921] **4**
Dimitrakov (1996)[859] **4**
Dimitriu (1968)[862] **4**
Dinda (1997)[865] **4**
Dinda (2001)[868] **7**
Dinda (2001)[871] **4**
Ditchburn (1990)[874] **4**
Dobrowolski (2002)[876] **4**
Dodge (1977)[879] **4**
Dolezel (2003)[882] **4**
Donaldson (1992)[885] **4**
Donohue (2004)[888] **4**
Dorio (1999)[891] **4**
Douzal (1995)[894] **4**
Dovey (1969)[897] **4**
Dowell (1990)[900] **7**
Dreisler (2002)[903] **4**
Driese (1966)[906] **4**
Droller (1998)[909] **4**
Du (1982)[912] **4**
Dumler (1989)[369] **2**
Dusek (1987)[915] **4**
Dutts (1970)[918] **4**
Edel (1989)[924] **2**
Eggensperger (1989)[927] **4**
Eichner (1990)[930] **4**
Eisenberger (1999)[933] **4**
Elton (1993)[936] **4**
Emamian (1996)[939] **4**
Enarson (1984)[942] **4**
Endres (1971)[945] **4**
Engel (1980)[948] **4**
Erlanson (1980)[951] **4**
Errando Smet (1996)[792] **4**
Escaf Barmadah (1998)[327] **6**
Eskelinen (1998)[954] **4**
Esposti (1969)[957] **4**
Etemad (2003)[960] **4**
Evans (1991)[963] **4**
Evans (1997)[966] **4**
Evans (2001)[969] **4**
Everaert (2003)[972] **4**
Ewert (1996)[975] **4**
Ezz el Din (1996)[978] **4**
Fair (1979)[981] **4**
Fairley (1993)[983] **4**
Fantl (1997)[986] **2**
Farthing (1999)[989] **4**
Fassett (1983)[992] **4**

continued

TABLE 5 *Studies excluded from the review and reasons for exclusion (cont'd)*

Favaro (1997)[995] **4**
Favre (1989)[998] **4**
Federle (1987)[1001] **4**
Feehally (1989)[1003] **4**
Feehally (1998)[1006] **4**
Feld (1997)[1009] **2**
Feldman (1968)[1012] **4**
Fernandez Gomez (2002)[1015] **4**
Ferrario (1989)[1021] **4**
Fickenscher (1999)[1024] **2**
Fielding (1997)[1027] **4**
Fielding (2002)[1030] **4**
Fillastre (1975)[1033] **4**
Finlayson (2000)[1036] **4**
Finney (1989)[1039] **4**
Fischer (1980)[1042] **7**
Fladerer (1984)[1045] **4**
Flamm (1992)[1048] **4**
Flanigan (1993)[1051] **4**
Flessland (2002)[1054] **4**
Flourie (2002)[1057] **4**
Flyger (1996)[1060] **4**
Fogazzi (1989)[1063] **4**
Fogazzi (1991)[1066] **4**
Fogazzi (1996)[1069] **2**
Fortune (1985)[1072] **4**
Fracchia (1995)[12] **7**
Free (1972)[1077] **4**
Freitag (1979)[1080] **4**
Freni (1977)[1083] **4**
Frick (1966)[1086] **4**
Frick (1978)[1089] **1**
Friedman (1995)[1092] **4**
Friedman (1996)[16] **4**
Fröhlich (1981)[1097] **4**
Froom (1984)[1100] **4**
Froom (1986)[1103] **4**
Froom (1987)[1106] **4**
Froom (1997)[1109] **4**
Froom (2004)[1112] **4**
Fuchs (1999)[1115] **4**
Fuchs (1990)[1117] **4**
Fünfstück (2000)[1120] **7**
Fünfstück (2000)[1123] **1**
Fuhrman (1993)[1126] **4**
Fuiano (2000)[1129] **4**
Fujita (1998)[1132] **4**
Furuya (2002)[1135] **4**
Gaca (1971)[1138] **4**
Gai (2002)[1141] **4**
Gai (2003)[1144] **4**
Gambrell (1996)[1147] **2**
Game (2001)[1150] **1**
Game (2002)[1153] **1**
Gangwal (1985)[1156] **7**
Garcia Garcia (2002)[1159] **4**
Gattegno (2000)[1162] **4**
Gauthier (1990)[1165] **4**
Gavant (1992)[1168] **4**
Geerdsen (1979)[1171] **4**
Georgopoulos (1996)[1174] **2**
Gerlag (1989)[1177] **4**
Geyer (1993)[1180] **4**
Ghali (1998)[1183] **4**
Gibbs (1990)[1186] **4**
Gillatt (1987)[1189] **4**
Gilloz (1989)[1192] **4**
Gimondo (1996)[1195] **4**
Giudicelli (1984)[1198] **4**
Glebski (1986)[1204] **4**
Gleich (1999)[1207] **4**
Gleizer (1973)[1210] **4**
Godec (1989)[592] **4**
Goessl (2001)[1213] **4**
Goldner (1984)[1216] **7**
Goldner (1985)[1219] **4**
Goldstein (1984)[1222] **4**
Goldwasser (1990)[1225] **4**
Golfieri (2002)[1228] **4**
Golfieri (2002)[1231] **4**
Golijanin (1995)[1234] **4**
Golijanin (2000)[1237] **4**
Golin (1980)[152] **4**
Gomes (2001)[155] **4**
Gontero (2002)[158] **4**
Goodman (1975)[164] **4**
Goonewardena (1998)[167] **4**
Gothlin (1988)[170] **4**
Gottsche (1989)[173] **4**
Gould (1992)[176] **4**
Graber (1987)[178] **4**
Graf (1993)[181] **2**
Graf (1994)[184] **7**
Gray (2001)[187] **7**
Greer (1985)[190] **4**
Grieshop (1995)[193] **4**
Griffen (1978)[196] **4**
Grooms (1973)[199] **4**
Grossfeld (1998)[15] **2**
Grossfeld (2001)[20] **2**
Grossfeld (2001)[11] **2**
Grossfeld (2001)[2] **4**
Grunfeld (2000)[210] **4**
Grzetic (1989)[213] **4**
Guder (1988)[216] **4**
Guder (1992)[219] **4**
Guder (1993)[221] **4**
Guder (1995)[224] **4**
Guder (1997)[227] **2**
Guder (1997)[230] **4**
Guder (2000)[803] **4**
Guder (2001)[233] **4**
Guice (1982)[236] **4**
Guice (1983)[239] **7**
Gupta (2000)[242] **4**
Guss (1985)[245] **4**
Gyory (1996)[248] **4**
Haas (1983)[251] **2**
Härtel (1972)[254] **5**
Häusermann (1979)[256] **6**
Haillot (1992)[259] **4**
Halachmi (1998)[262] **4**
Hall (1995)[265] **4**
Hall (1999)[268] **2**
Hall (2003)[271] **4**
Halling (2002)[274] **7**
Halsell (1987)[277] **4**
Hamm (2002)[280] **4**
Hammoud (2001)[283] **4**
Handmaker (1975)[286] **4**
Hanna (1997)[289] **4**
Hansen (1981)[292] **4**
Hardeman (1987)[295] **7**
Hardeman (1987)[298] **4**
Harkness (1975)[301] **4**
Harper (2001)[304] **2**
Harr (1995)[307] **4**
Harris (1971)[310] **4**
Harris (1975)[313] **4**
Harris (2001)[316] **4**
Harris (2002)[319] **4**
Harzmann (1987)[322] **4**
Hasan (1994)[325] **4**
Hastie (1994)[328] **4**
Hattori (1990)[331] **4**
Hattori (1991)[334] **4**
Hattori (1993)[337] **4**
Haug (1985)[340] **4**
Hauglustaine (1982)[215] **4**
Hayashi (1987)[343] **4**
Hedelin (2001)[346] **4**
Heering (1990)[349] **2**
Heine (2003)[352] **2**
Henderson (1998)[355] **4**
Hendler (1972)[358] **4**
Hermansen (1989)[361] **4**
Herschorn (1991)[364] **4**
Hertel (1973)[367] **4**
Herts (2003)[370] **4**
Hertz (1967)[373] **4**
Hewitt (1997)[376] **4**
Hiatt (1994)[379] **4**
Hiatt (1994)[7] **4**
Hidaka (1989)[384] **4**
Hinchliffe (1996)[387] **4**
Hoffmann (1976)[390] **7**
Hofmann (1991)[393] **4**
Hofmann (1991)[396] **2**
Hofmann (1992)[399] **4**
Hofmann (1994)[402] **7**
Holmquist (1981)[405] **4**
Holmquist (1984)[408] **4**
Holtl (2001)[411] **2**
Hong (2001)[870] **4**
Hoque (2003)[414] **4**
Hotta (1992)[417] **4**
Hotta (1994)[420] **4**
Hotta (1996)[423] **4**
Hotta (1998)[426] **4**
Hotta (2000)[429] **4**
Houppermans (2001)[432] **4**
Houston (1988)[435] **7**
Howard (1990)[437] **4**

continued

TABLE 5 *Studies excluded from the review and reasons for exclusion (cont'd)*

Howard (1991)[440] **4**
Hrvacevic (1994)[446] **4**
Hsu (2000)[449] **4**
Hubbell (1986)[451] **4**
Huebner (1990)[454] **4**
Hueston (1995)[457] **7**
Hughes (1988)[460] **4**
Huland (1989)[463] **4**
Hungerhuber (2001)[466] **4**
Huussen (2003)[469] **4**
Huussen (2003)[472] **4**
Huussen (2004)[475] **2**
Hvidt (1973)[478] **4**
Hyodo (1991)[481] **4**
Hyodo (1993)[484] **7**
Hyodo (1994)[487] **4**
Hyodo (1995)[489] **1**
Hyodo (1996)[492] **1**
Iczkowski (2001)[495] **4**
Iga (1997)[498] **4**
Iizuka (1986)[501] **4**
Imai (1992)[504] **4**
Indudhara (1996)[1211] **4**
Isorna (1981)[507] **4**
Ito (1990)[510] **4**
Ivandic (1996)[513] **4**
Iversen (1977)[516] **4**
Izzedine (2001)[519] **4**
Jacobellis (1982)[522] **4**
Jacobellis (1983)[525] **4**
Jaffe (2001)[528] **2**
Jaffe (2004)[531] **4**
Jagenburg (1980)[534] **4**
Jagjivan (1988)[537] **4**
Jakubowska-Kuzmiuk (1994)[540] **4**
Jalalah (2000)[543] **4**
Jalalah (2002)[545] **4**
Janssens (1992)[548] **4**
Janssens (1994)[551] **4**
Jardin (1970)[554] **4**
Jardine (2000)[557] **4**
Jaros (1974)[560] **4**
Jarvis (1998)[563] **4**
Jewett (1973)[566] **4**
Ji (2001)[1191] **7**
Jinde (2003)[569] **4**
Johnston (1997)[572] **7**
Jones (1988)[575] **4**
Jones (1988)[578] **4**
Jones (1989)[581] **4**
Jones (1990)[584] **7**
Jones (1992)[587] **4**
Jones (1997)[590] **4**
Jones (1997)[593] **4**
Jonsson (1972)[596] **4**
Jonsson (1976)[599] **4**
Jou (1998)[602] **4**
Jubelirer (1993)[605] **4**
Jungers (1980)[608] **4**
Juul (1989)[611] **4**
Kahan (1981)[614] **7**
Kakehi (1999)[617] **4**
Kallmeyer (1992)[620] **7**
Kamoi (1996)[623] **4**
Kamoi (1996)[626] **4**
Kang (2003)[629] **4**
Kannan (1999)[632] **4**
Kaplan (1997)[635] **4**
Kartavenko (1977)[637] **4**
Kasinath (1996)[640] **2**
Kawada (1994)[643] **4**
Kawakita (1996)[646] **4**
Kawamura (1995)[649] **5**
Kazmin (1969)[652] **4**
Keay (2001)[655] **4**
Keir (2002)[658] **4**
Kennedy (1988)[661] **4**
Kerbl (2000)[664] **4**
Kerr (1999)[667] **4**
Kesson (1978)[670] **4**
Khadra (2000)[14] **4**
Khadra (2001)[675] **4**
Khan (2002)[678] **4**
Khochikar (1996)[681] **7**
Kiel (1987)[684] **4**
Kim (1998)[687] **4**
Kincaid-Smith (1982)[690] **4**
Kincaid-Smith (1987)[693] **4**
Kinders (2002)[696] **4**
Kirsh (1999)[782] **4**
Kirsztajn (2002)[699] **4**
Kisa (1986)[701] **4**
Kitahara (2002)[704] **4**
Kitamoto (1993)[707] **7**
Klein (1988)[709] **4**
Klein (1988)[712] **4**
Klein (1998)[715] **4**
Klein (1998)[717] **4**
Knight (2003)[720] **4**
Knottnerus (1995)[723] **4**
Knottnerus (1985)[726] **4**
Knottnerus (1992)[729] **4**
Knottnerus (1992)[732] **4**
Knottnerus (2002)[735] **4**
Knudson (1992)[738] **4**
Kobayashi (1992)[741] **4**
Kobayashi (2003)[744] **4**
Köhler (1975)[747] **4**
Köhler (1999)[750] **4**
Koene (1992)[753] **4**
Koene (1997)[756] **4**
Koenig (1999)[759] **7**
Konishi (1985)[762] **4**
Kosciow (1995)[765] **4**
Kourambas (2000)[767] **4**
Kouriefs (2000)[770] **4**
Kowalchuk (1998)[773] **4**
Kozlovskaia (1975)[776] **4**
Kreel (1974)[779] **4**
Krupski (1996)[785] **4**
Kudish (1975)[788] **4**
Kumanov (1993)[791] **4**
Kupor (1975)[794] **4**
Kutter (1976)[797] **4**
Kutter (1980)[800] **4**
Lafuente (1998)[806] **4**
Lahme (2001)[809] **4**
Laissy (2001)[812] **4**
Lam (1995)[815] **4**
Lammers (2001)[818] **4**
Lammle (2002)[821] **4**
Lance (1998)[824] **4**
Landman (1998)[827] **4**
Landwehr (1978)[830] **4**
Lang (2000)[833] **4**
Lang (2003)[836] **4**
Lang (2003)[839] **4**
Lang (2003)[845] **4**
Lang (2004)[842] **7**
Lano (1979)[848] **4**
Lapointe (1984)[851] **4**
Laufer (1992)[854] **4**
Laville (1991)[857] **4**
Laville (1992)[860] **4**
Lawrence (1995)[863] **3**
Le Floch (2001)[866] **4**
Lee (1981)[869] **4**
Lee (1993)[872] **4**
Lee (2000)[875] **4**
Lee (2001)[877] **4**
Leibovici (1989)[880] **4**
Lent (1975)[883] **4**
Leopold (1973)[886] **4**
Lesak (1986)[889] **4**
Lessin (1974)[892] **4**
Lewis (1976)[895] **6**
Lewis-Jones (1989)[898] **7**
Leyh (1988)[901] **2**
Li (1984)[904] **4**
Li (1987)[907] **4**
Li (1995)[910] **1**
Lin (2001)[913] **4**
Lindell (2000)[916] **2**
Little (2000)[919] **4**
Litwin (1985)[922] **4**
Lloyd Davies (1989)[925] **4**
Lohr (1968)[1121] **4**
Lokeshwar (2001)[928] **4**
Loo (1986)[931] **4**
Loosemore (1991)[934] **4**
Lopez Cubillana (2002)[937] **4**
Lorenzo Gomez (2003)[940] **4**
Lorenzo Gomez (2003)[943] **4**
Loria (2002)[946] **4**
Lott (1995)[949] **4**
Low (1972)[952] **4**
Lowe (1989)[955] **4**
Lowe (1996)[958] **4**
Loze (1984)[961] **4**
Lubec (1984)[964] **4**
Luchs (2002)[967] **4**
Lundin (2003)[973] **4**
Lutzeyer (1981)[976] **4**

continued

TABLE 5 *Studies excluded from the review and reasons for exclusion (cont'd)*

Lutzeyer (1981)[979] **4**
Luzzatto (1994)[984] **4**
Luzzatto (1994)[987] **4**
Lwaleed (2000)[990] **4**
Lynch (1994)[993] **4**
Lynch (1994)[996] **4**
Machida (1977)[999] **4**
Machida (1983)[1002] **4**
Mack (1986)[1004] **4**
Mack (1987)[1007] **4**
Madersbacher (1968)[1010] **4**
Madsen (1995)[1013] **4**
Maher (2004)[1016] **2**
Mahnert (1999)[1019] **4**
Mahnert (2003)[1022] **6**
Mallick (1984)[1025] **2**
Malmström (2003)[1028] **4**
Malmström (2003)[1031] **4**
Malone (1994)[1034] **4**
Mangin (1990)[1037] **4**
Mann (1987)[1040] **4**
Mansat (1983)[1043] **7**
Mariani (1984)[1046] **7**
Mariani (1989)[1049] **3**
Markova (1989)[1014] **4**
Marumo (2002)[1052] **4**
Mason (1990)[1055] **4**
Mason (1992)[1058] **4**
Matthews (1983)[1061] **4**
Matz (1981)[1064] **4**
Mayayo Dehesa (1995)[820] **4**
Mayfield (1998)[1067] **4**
Mazhari (2002)[1070] **2**
Mazouz (2003)[1073] **4**
McAndrew (1994)[1075] **4**
McCarthy (1997)[1078] **2**
McCook (1982)[1081] **4**
McDonald (1976)[1084] **4**
McGinley (1992)[1087] **4**
McGregor (1998)[1090] **4**
McLarty (2002)[1093] **4**
McLean (1969)[1095] **4**
McNicholas (1998)[1098] **4**
McQueen (1993)[1101] **4**
Mee (1989)[1107] **4**
Mehta (1994)[1110] **4**
Melamed (1990)[1113] **4**
Meleg-Smith (2001)[1116] **4**
Melissourgos (2002)[1118] **4**
Mendelson (2003)[1124] **4**
Messing (1989)[1127] **4**
Messing (1990)[1130] **4**
Messing (1992)[1133] **7**
Messing (1995)[1136] **4**
Messing (1995)[1139] **4**
Meuleman (1988)[1145] **4**
Mian (2000)[1148] **4**
Michael (1976)[1151] **4**
Michel (1984)[1154] **4**
Miguel-Gomara Perello (1993)[403] **4**
Milheiro (1999)[1157] **4**
Miller (1993)[1160] **4**
Miller (1994)[1163] **4**
Miller (1995)[1166] **4**
Miltenyi (1984)[1169] **5**
Minami (1969)[1172] **4**
Minana Lopez (1993)[1175] **4**
Misdraji (1996)[1178] **4**
Mishra (2001)[1181] **4**
Mishra (2003)[1184] **7**
Mishra (2004)[1187] **5**
Miura (1990)[1190] **4**
Miura (2001)[1193] **4**
Mkrtchian (1989)[1196] **4**
Modder (1994)[1199] **4**
Mohr (1986)[1202] **4**
Mohr (1987)[1205] **4**
Mokulis (1995)[1208] **4**
Moll (1994)[1214] **4**
Moller (1995)[1217] **4**
Mombaerts (1966)[1220] **4**
Monhart (1993)[1223] **4**
Monsallier (1990)[1226] **4**
Monstrey (1988)[1229] **4**
Montanari (1993)[1232] **4**
Moore (1988)[1235] **4**
Moran (1996)[1238] **4**
Morel Journel (2002)[153] **4**
Morel-Maroger (1969)[156] **4**
Morewood (1986)[159] **4**
Morgan (2000)[162] **7**
Morimoto (2003)[165] **4**
Morozov (1987)[171] **4**
Morrison (1975)[174] **4**
Moses (1993)[44] **4**
Muehrcke (1969)[179] **4**
Mukherjee (1998)[191] **4**
Müller (1988)[182] **4**
Müller (1989)[185] **7**
Müller-Wiefel (1978)[188] **5**
Munoz Velez (1998)[194] **4**
Nabi (2003)[200] **4**
Nabi (2004)[202] **4**
Nadasdy (1989)[204] **4**
Nagar (2000)[206] **4**
Nagel (1968)[208] **4**
Nagy (1985)[211] **4**
Nakada (1995)[214] **4**
Nakamura (1981)[217] **4**
Nasuti (1999)[24] **4**
Navani (1968)[225] **4**
Nelde (1998)[228] **4**
Newhouse (2000)[231] **2**
Newsam (1966)[234] **4**
Ng (1984)[237] **2**
Nickel (1991)[240] **4**
Niemi (1984)[243] **4**
Nieuwhof (1996)[246] **4**
Nieuwhof (1999)[249] **4**
Nikolaev (1982)[252] **4**
Nishikawa (1992)[13] **4**
Nishimura (2000)[257] **4**
Nisman (2000)[260] **4**
Nisman (2002)[263] **4**
Notley (1969)[266] **4**
Novicki (1998)[269] **3**
Nozaki (1998)[272] **4**
Nyman (1997)[275] **4**
Nystrom (1973)[278] **4**
O'Brien (1987)[281] **4**
Obroniecka (1998)[1102]
Ody (1986)[284] **4**
Oehr (2004)[287] **7**
Örsten (1971)[290] **4**
Offringa (1992)[293] **4**
Oge (2002)[296] **4**
Ojs (2002)[299] **4**
Okada (1989)[302] **4**
Okada (2001)[305] **4**
Oktenli (1999)[308] **4**
Oktenli (2000)[311] **4**
Oliech (1998)[314] **4**
Olivo (1989)[317] **4**
Oppelt (1970)[320] **4**
Orell (1969)[323] **4**
Osegbe (1984)[326] **4**
Oser (1993)[329] **4**
Osmani (1987)[332] **7**
Osten (1972)[335] **4**
Ota (1992)[338] **4**
Otnes (1980)[341] **4**
Overgaard (1966)[344] **4**
Palmer (1998)[347] **4**
Panchev (1997)[350] **4**
Paola (1990)[353] **2**
Paone (1981)[356] **4**
Papanicolaou (1986)[359] **4**
Pardo (1975)[362] **4**
Pardo (1977)[365] **4**
Pardo (1979)[368] **4**
Parmar (2003)[371] **4**
Pascual (1990)[374] **4**
Pashos (2002)[377] **4**
Patard (1996)[380] **4**
Patel (1997)[382] **4**
Paul (1993)[385] **4**
Peacock (2001)[388] **4**
Pearce (2001)[391] **4**
Pellet (1980)[404] **4**
Pellet (1981)[397] **4**
Peng (1999)[400] **7**
Peres (1990)[406] **4**
Perlman (1996)[409] **7**
Perry (1989)[412] **4**
Pettersson (1990)[415] **2**
Pettersson (1990)[418] **4**
Phillips (2001)[421] **4**
Piccoli (1988)[424] **4**
Pirtskalaishvili (1999)[427] **4**
Plail (1990)[430] **4**
Pode (1998)[433] **4**
Pode (1999)[23] **4**
Poliak (1977)[438] **4**

continued

TABLE 5 *Studies excluded from the review and reasons for exclusion (cont'd)*

Pollastri (1992)[441] **5**
Pollock (1989)[444] **7**
Pompeius (1984)[447] **4**
Ponsky (2001)[27] **4**
Porri (1980)[452] **4**
Potter (1999)[455] **4**
Power (1982)[458] **4**
Powers (1991)[461] **4**
Press (1995)[464] **4**
Prokopiuk (2002)[467] **2**
Punt (1984)[470] **4**
Punt (1989)[473] **4**
Puppo (1991)[476] **4**
Qin (1996)[479] **4**
Quenu (1985)[482] **4**
Racki (2003)[485] **4**
Rahman (2001)[488] **4**
Raica (1997)[490] **4**
Ramakumar (2000)[493] **4**
Raman (1986)[496] **7**
Rao (1989)[499] **4**
Ratobylskii (1994)[505] **4**
Ratobylsky (1994)[508] **4**
Ravery (1998)[511] **4**
Reichelt (2001)[514] **4**
Restrepo (1989)[517] **4**
Reynard (2000)[520] **4**
Richards (1997)[523] **4**
Richards (1998)[526] **4**
Richards (1999)[529] **4**
Richter (2002)[532] **4**
Rimondini (2001)[535] **4**
Rinsho (1984)[538] **4**
Rischmann (2002)[541] **4**
Ritchie (1986)[6] **4**
Rivas del Fresno (1995)[546] **4**
Rizzoni (1983)[549] **5**
Rizzoni (1983)[552] **5**
Rockall (1997)[555] **2**
Rodrigues Netto (1977)[558] **4**
Rodriguez Castellanos (2000)[561] **4**
Roebuck (1999)[564] **4**
Roehrborn (1986)[567] **7**
Rosales (1992)[570] **4**
Rossi (1988)[573] **4**
Roth (1991)[576] **4**
Roth (1992)[579] **4**
Roth (1995)[582] **4**
Rotkopf (1992)[585] **2**
Rotkopf (1993)[588] **4**
Rotkopf (1993)[591] **2**
Rous (1985)[594] **4**
Rowbotham (2001)[597] **2**
Roy (1993)[600] **4**
Royal (2000)[603] **4**
Rüttimann (1990)[606] **4**
Ruiz-Deya (2001)[609] **7**
Ryckelynck (1991)[612] **4**
Saito (2003)[615] **4**
Salm (1969)[618] **4**
Saltzman (1998)[621] **4**
Sanchez Carbayo (2001)[624] **4**
Sandler (1995)[627] **4**
Sandler (2000)[630] **4**
Sandoz (1988)[633] **2**
Sandoz (1988)[636] **2**
Sandoz (1988)[638] **2**
Sangtani (2003)[641] **4**
Sarosdy (2001)[644] **4**
Sarsody (1997)[647] **4**
Sasaki (1993)[650] **4**
Sato (1986)[653] **4**
Saunders (2002)[656] **4**
Saunders (2002)[659] **4**
Savige (2002)[662] **4**
Savioli (1993)[665] **4**
Saxena (1992)[668] **5**
Saxena (1996)[671] **4**
Scarpero (2000)[673] **4**
Schattner (1990)[676] **4**
Schifferli (1979)[679] **4**
Schiffleri (1982)[682] **4**
Schiwara (1988)[685] **4**
Schmidt (1988)[688] **2**
Schmiedt (1976)[691] **2**
Schoeppe (1982)[694] **2**
Schoolwerth (1987)[697] **2**
Schramek (1985)[700] **6**
Schramek (1989)[702] **4**
Schramek (1990)[705] **4**
Schroder (1994)[19] **2**
Scialabba (1992)[710] **7**
Segal (1998)[713] **4**
Sellin (1982)[716] **4**
Sells (2001)[718] **4**
Sergeyev (1998)[721] **7**
Sharfi (1994)[724] **4**
Sharma (1999)[727] **4**
Shcherbin (1985)[730] **4**
Sheley (1999)[733] **4**
Shenoy (1985)[736] **4**
Shetye (2003)[739] **4**
Shichiri (1986)[742] **4**
Shichiri (1986)[745] **4**
Shichiri (1988)[748] **4**
Shield (2000)[751] **4**
Shinohara (1991)[754] **4**
Shpigel (1991)[757] **4**
Siemer (2000)[760] **4**
Sigler (1986)[763] **4**
SIGN (1997)[3] **2**
Simon (2003)[768] **4**
Simpson (1977)[771] **4**
Simpson (1991)[774] **4**
Simpson (1992)[777] **4**
Simpson (1996)[780] **4**
Sinclair (1993)[783] **4**
Singh (1999)[786] **4**
Sinniah (1976)[789] **4**
Smith (1978)[795] **4**
Sobh (1993)[798] **4**
Sokolosky (2001)[801] **4**
Soltes (1988)[804] **4**
Sozen (2003)[807] **4**
Sparwasser (1994)[810] **2**
Spencer (1990)[813] **4**
Spencer (1990)[816] **7**
Spencer (1990)[819] **4**
Stacul (2003)[822] **4**
Stapleton (1987)[527] **4**
Stark (1999)[825] **4**
Starling (1997)[828] **7**
Steiger (2000)[831] **2**
Stewart (1990)[834] **4**
Stirati (1989)[837] **2**
Stoeber (2002)[840] **4**
Stollerman (2001)[843] **4**
Strauss (1981)[846] **4**
Studer (2003)[849] **4**
Su (2003)[852] **4**
Sugaya (1991)[855] **4**
Sugimura (2001)[858] **4**
Suhler (1972)[861] **4**
Suleiman (1987)[864] **4**
Summerton (2002)[867] **7**
Sutton (1990)[873] **4**
Sutton (1990)[31] **2**
Suzuki (1995)[878] **4**
Suzuki (2000)[881] **4**
Swischuk (1990)[884] **4**
Syed (2002)[887] **4**
Syme (1979)[890] **4**
Szewczyk (1989)[893] **4**
Talbot (1984)[896] **4**
Tamaki (1983)[899] **4**
Tanaka (1993)[902] **4**
Tanaka (1996)[905] **4**
Tasic (2001)[908] **4**
Taube (1998)[911] **4**
Tawfiek (1997)[914] **4**
Tawfiek (1998)[917] **4**
Tejani (1982)[920] **4**
Texter (1980)[923] **4**
Thal (1986)[926] **4**
Thaller (1999)[929] **2**
Thiel (1986)[932] **4**
Thiel (2004)[935] **4**
Thomas (1980)[938] **4**
Thomason (1989)[941] **4**
Thompson (1986)[944] **2**
Thompson (1987)[947] **4**
Tiebosch (1989)[950] **4**
Tieng (1998)[953] **3**
Tönies (1985)[956] **7**
Tomimoto (1991)[959] **4**
Tomson (2002)[962] **4**
Topf (1977)[965] **2**
Topham (1994)[968] **4**
Topham (1994)[971] **2**
Topham (1997)[974] **4**
Topham (2004)[977] **4**
Topsakal (2001)[980] **4**
Tosaka (1990)[982] **4**

continued

TABLE 5 *Studies excluded from the review and reasons for exclusion (cont'd)*

Tosana (1989)[985] **4**
Trabelsi (1985)[988] **4**
Truniger (1985)[994] **4**
Truniger (1987)[997] **2**
Tschan (1975)[1000] **7**
Tsoufakis (2000)[1005] **2**
Tsujii (2001)[1008] **4**
Tsukahara (1992)[1011] **5**
Tummers (1973)[991] **4**
Turton (1980)[1017] **4**
Twyman (1995)[1020] **4**
Ubels (1999)[1023] **4**
Uehara (1986)[1026] **4**
Ueno (1991)[1029] **4**
US Preventative Services T F (1990)[1032] **4**
Valdes (1987)[1035] **4**
Vallancien (1985)[1038] **4**
Valles (1988)[1041] **4**
Van de Putte (1973)[1044] **4**
Van de Putte (1974)[1047] **4**
van den Ouden (2000)[1050] **4**
van der Snoek (1994)[1053] **5**
Van de Putte (1974)[1056] **4**
Vanderschueren (2002)[1059] **4**
Vanrenteerghem (1986)[1062] **4**
Vastenburg (1976)[1065] **4**
Vaur (1974)[1068] **4**
Vehaskari (1989)[1071] **4**
Vehaskari (1990)[1074] **4**
Verwiebe (1993)[1076] **4**
Viguier (1994)[1079] **4**
Vlahou (2002)[1082] **4**
Wah (2001)[1085] **4**
Wakui (2000)[1088] **4**
Walb (1986)[1091] **4**
Walker (1993)[1094] **4**
Wallace (1993)[1096] **4**
Walter (1996)[1099] **4**
Watanabe (1996)[1105] **4**
Watson (1998)[1108] **4**
Watson (2002)[443] **4**
Wauters (1987)[1111] **4**
Wawroschek (2003)[1114] **4**
Weatherall (1996)[1] **4**
Weaver (1983)[1119] **4**
Webb (1997)[1122] **4**
Weissbach (1971)[1125] **4**
Whisnant (1979)[1128] **4**
Wiener (1993)[1131] **4**
Wilson (1975)[1134] **4**
Winkler (1997)[1137] **2**
Wirnsberger (1998)[1140] **7**
Woess (1987)[1143] **6**
Wolfish (1987)[1146] **4**
Wong (1996)[1149] **6**
Woolhandler (1989)[1152] **4**
Wyndaele (2004)[1155] **2**
Yamagata (1996)[1158] **4**
Yamagata (2002)[1161] **4**
Yamamoto (1993)[1164] **4**
Yasumasu (1994)[1167] **4**
Yazaki (1991)[1170] **4**
Ye (2004)[1173] **4**
Yip (1998)[1176] **2**
Yip (1998)[1179] **4**
Yip (2000)[1182] **4**
Yip (2000)[1185] **4**
Yokoyama (1996)[1188] **4**
Ysteng (1986)[1194] **4**
Yu (1999)[1197] **4**
Zagoria (1995)[1200] **4**
Zakrzewski (1972)[1203] **4**
Zama (1990)[1206] **4**
Zaman (2001)[1209] **4**
Zeitlin (1996)[1212] **4**
Zeitlin (1996)[1215] **4**
Zerat (1988)[1218] **7**
Zhang (1997)[1221] **7**
Zielinski (1973)[1224] **4**
Zilva (1985)[1227] **4**
Zimmermann (2000)[1230] **2**
Zingg (1968)[1233] **7**
Zippe (1999)[1236] **4**
Zoelly (1992)[1239] **2**

Chapter 6

Results of the review

Results of the literature searches

The literature searches identified over 12,000 references. These were screened for relevance and 1243 references were considered to be potentially relevant. Copies of 18 of these articles could not be obtained during the review.[22,715,720,921,922,1240–1252] A Czech article appeared to meet relevance criteria but as no translator was available this paper could not be assessed for inclusion.[1253] A total of 1226 articles were assessed for inclusion in the review. *Figure 1* shows the flow of studies through the review process and the number of studies excluded according to each of the inclusion criteria. Chapter 5 lists the studies excluded from the review.

A total of 118 studies met the inclusion criteria (including eight economic evaluations); 22 examined the diagnostic accuracy of tests to determine the presence of haematuria, six examined the diagnostic accuracy of the presence of haematuria in determining the presence of disease and 82 examined the diagnostic accuracy of tests used to investigate the underlying cause of haematuria. Five studies that met the inclusion criteria based on their English abstracts could not be extracted as they were published in languages for which translators could not be found. Three that met the inclusion criteria for tests to establish the presence of haematuria were in Swedish[1254,1255] and Danish.[1256] Two studies that met the inclusion criteria for investigation of the underlying cause of haematuria were in Russian.[1257,1258] Hence, 19 studies of tests to establish the presence of haematuria, six studies of haematuria as a diagnostic test for other disease states and 80 studies of tests to investigate the underlying cause of haematuria were included. Studies of tests to establish the presence of haematuria included 35 data sets, studies of haematuria as a diagnostic test for other disease states included 12 data sets and studies of tests to determine the underlying cause of haematuria included 192 data sets. A total of 239 data sets were therefore included in the review. Eight studies provided data on economic evaluation.

A total of 25 non-English language papers were included in this review: five French,[50,52,83,94,103] 11 German,[51,57,60,61,66,74,91,95,111,117,146] four Japanese,[29,98,135,1259] two Polish,[109,118] one Spanish,[80] one Portuguese[96] and one Dutch.[102]

Where insufficient details were reported, authors were contacted to provide further information. For example, authors were contacted if the study was published as an abstract, or if it appeared that 2×2 table data should be available for the study, but it was not extractable from the published report. A total of 18 authors were contacted requesting clarification or further details of data reported in published articles or abstracts or details of studies entered on research registers. No reply provided additional data for this review.

Efficacy of diagnostic algorithms for the investigation of haematuria

No studies that evaluated the efficacy of a diagnostic algorithm and met the inclusion criteria were identified.

Effectiveness of screening for haematuria

No trials evaluating the effectiveness of screening for haematuria were identified.

Effectiveness of further investigation of haematuria

No trials evaluating the effectiveness of investigations to determine the underlying cause of haematuria were identified.

Diagnosis of haematuria

Nineteen studies evaluated tests to determine the presence or absence of haematuria. With the exception of one study that compared different microscopy techniques (*Table 6*),[53] all studies evaluated the diagnostic performance of dipstick tests (see *Table 7*).

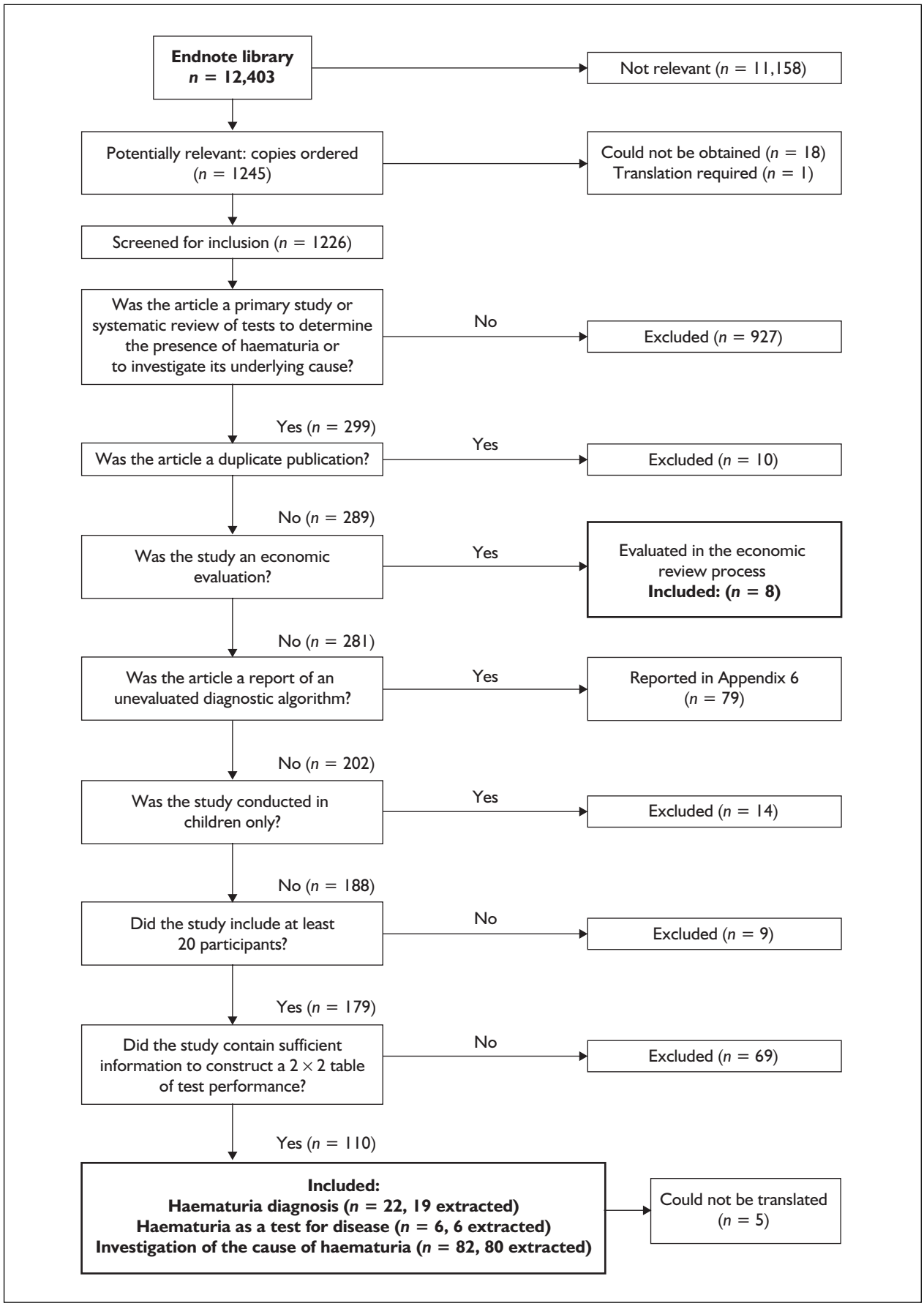


FIGURE 1 *Flow chart of studies through the review process*

TABLE 6 *Results of other studies of tests for the detection of haematuria*

Study details	Index test (+ve test)	Reference test (+ve test)	TP	FP	FN	TN	Sensitivity	Specificity	LR+	LR–	DOR
Froom (1987)[53]	Microscopy (HPF) (≥3 RBCs/HPF)	Microscopy (>5000 RBCs/ml)	35	32	4	1256	89.7	97.5	36.1	0.11	343.4
	Microscopy (HPF) (≥1 RBC/HPF)	Microscopy (>5000 RBCs/ml)	39	50	0	1238	100.0	96.1	25.8	0.00	NC
	Microscopy (HPF) (≥3 RBCs/HPF)	Microscopy (>2000 RBCs/ml)	63	4	53	1207	54.3	99.7	164.4	0.46	358.7
	Microscopy (HPF) (≥1 RBC/HPF)	Microscopy (>2000 RBCs/ml)	73	16	43	1195	62.9	98.7	47.6	0.38	126.8

Column headings in this and subsequent tables: DOR, diagnostic odds ratio; EP, false positives; FN, false negatives; LR–, negative-likelihood ratio; LR+, positive likelihood ratio; TN, true negatives; TP, true positives.
NC, not calculated, zero denominator.

TABLE 7 *Results of studies of dipstick tests for the detection of haematuria*

Study details	Index test (+ve test)	Reference test (+ve test)	TP	FP	FN	TN	Sensitivity	Specificity	LR+	LR–	DOR
Arm (1986)[49]	N-Multistix-SG (trace, +, ++, or +++)	Microscopy (≥ 10 RBCs/μl)	438	47	83	257	84.1	84.5	5.4	0.19	28.9
Bonard (1986)[50]	N-Multistix	Microscopy (≥ 10 RBCs/μl)	156	22	83	988	65.3	97.8	30.0	0.36	84.4
Braun (1975)[51]	Sangur-Test (>5 RBCs/μl)	Microscopy (>5 RBCs/hpf)	145	74	0	420	100.0	85.0	6.7	0.00	NC
	Sangur-Test (any RBCs)	Microscopy (>5 RBCs/hpf)	145	179	0	315	100.0	63.8	2.8	0.00	NC
Demol (1980)[52]	Bili-Labstix	Microscopy (≥ 10 RBCs/hpf)	10	9	8	73	55.6	89.0	5.1	0.50	10.1
Gibson (1986)[54]	Multistix (>Trace)	Microscopy (≥ 10^6 cells/L)	31	8	10	51	75.6	86.4	5.6	0.28	19.8
Gleeson (1993)[55]	Reagent strip test (trace, 1+, 2+. 3+ or 4+)	Microscopy (≥ 5 RBCs/μl)	185	98	30	687	86.0	87.5	6.9	0.16	43.2
Grinstead (1987)[56]	Clinitek 200/Multistix 9 (≥ trace)	Microscopy (≥ 1 RBC/hpf)	50	13	34	207	59.5	94.1	10.1	0.43	23.4
	Clinitek 200/Multistix 9 (≥ trace)	Microscopy (≥ 4 RBCs/hpf)	38	25	11	230	77.6	90.2	7.9	0.25	31.8
Gruhn (1974)[57]	N-Labstix	Other (presence of haemoglobin)	44	3	0	46	100.0	93.9	16.3	0.00	NC
Holland (1995)[58]	Multistix-10 (read visually)	Microscopy (≥ 10^6 cells/l)	785	465	188	1490	80.7	76.2	3.4	0.25	13.4
	Multistix-10 (read by photometry)	Microscopy (≥ 10^6 cells/l)	816	583	157	1372	83.9	70.2	2.8	0.23	12.2
	Combur-10 (read visually)	Microscopy (≥ 10^6 cells/l)	766	353	207	1602	78.7	81.9	4.4	0.26	16.8
Jaffe (1979)[59]	Multistix [slight (1+), moderate (2+) or marked (3+) haematuria]	Microscopy (>20 RBCs/hpf)	365	786	33	8389	91.7	91.4	10.7	0.09	118.1

continued

TABLE 7 *Results of studies of dipstick tests for the detection of haematuria (cont'd)*

Study details	Index test (+ve test)	Reference test (+ve test)	TP	FP	FN	TN	Sensitivity	Specificity	LR+	LR–	DOR
	Multistix [slight (1+), moderate (2+) or marked (3+) haematuria]	Microscopy (>1 RBC/hpf)	832	319	773	7649	51.8	96.0	12.9	0.50	25.8
	Multistix [slight (1+), moderate (2+) or marked (3+) haematuria]	Microscopy (>5 RBCs/hpf)	638	513	184	8238	77.6	94.1	13.2	0.24	55.7
Kutter (1974)[61]	Sangur-Test	Microscopy	133	83	37	621	78.2	88.2	6.6	0.25	26.9
Kutter (1980)[60]	Combur-8 (any RBCs)	Microscopy (≥5 RBCs)	90	16	2	511	97.8	97.0	32.2	0.02	1437.2
McGlone (1990)[62]	Ames SG10	Microscopy (any RBCs)	182	260	47	591	79.5	69.4	2.6	0.30	8.8
Messing (1987)[63]	(≥trace)	Microscopy (≥2 RBCs/hpf)	60	1	6	109	90.9	99.1	100.0	0.09	1090.0
Ooi (1998)[64]	Combur 9 (≥1 RBC or haemoglobin)	Microscopy (>5 RBCs/hpf for males, and >10 RBC/hpf for females)	77	37	0	8	100.0	17.8	1.2	0.00	NC
Shaw (1985)[65]	Multistix (trace, 1+ or 2+)	Microscopy (any RBCs)	43	1	61	51	41.3	98.1	21.5	0.60	36.0
	Multistix (trace, 1+ or 2+)	Microscopy (≥1 RBC/hpf)	34	10	20	92	63.0	90.2	6.4	0.41	15.6
	Chemstrip 9 (trace, 1+ or 2+)	Microscopy (≥1 RBC/hpf)	41	11	13	91	75.9	89.2	7.0	0.27	26.1
	Chemstrip 9 (2+ RBCs)	Microscopy (≥1 RBC/hpf)	18	2	36	100	33.3	98.0	17.0	0.68	25.0
	Multistix (2+ RBCs)	Microscopy (≥1 RBC/hpf)	11	0	43	102	20.4	100.0	NC	0.80	NC
	Chemstrip 9 (≥ 1 RBC)	Microscopy (≥1 RBC/hpf)	22	2	32	100	40.7	98.0	20.8	0.60	34.4
	Multistix (≥ 1 RBC)	Microscopy (≥1 RBC/hpf)	12	0	42	102	22.2	100.0	NC	0.78	NC
	Chemstrip 9 (Trace, 1+ or 2+)	Microscopy (any RBCs)	51	1	53	51	49.0	98.1	25.5	0.52	49.1
Wawroschek (1998)[66]	Combur 9	Microscopy (>3 RBCs/hpf)	164	31	15	41	91.6	56.9	2.1	0.15	14.5
Yoo (1995)[67]	Uriflet (>+)	Microscopy (>5 RBCs/hpf)	186	255	6	783	96.9	75.4	3.9	0.04	95.2

NC, not calculated, zero denominator.

Dipstick tests (reagent strip tests)

A total of 18 studies reporting 31 data sets evaluated dipstick tests for the diagnosis of haematuria.[49–52,54–67] Thirteen (72%) of these studies either did not include an appropriate spectrum of patients or did not report sufficient details of the patient spectrum, and 14 (78%) failed to describe patient selection criteria adequately. Avoidance of test review bias was poorly reported, with 13 studies not reporting any information on blinding of investigators to results. Fourteen of the 18 dipstick studies did not report any information on the potential for clinical review bias. The full results of QUADAS evaluation for studies assessing the diagnostic accuracy of tests for haematuria are presented in *Table 8*.

All but one of the studies evaluated dipstick tests against a reference standard of microscopy. The exception was a 30-year-old East German study comparing 'N-Labstix' reagent strips against a reference standard of 'reagnost tablets', reporting a sensitivity of 100% and specificity of 94%.[57] Data from the remaining 17 studies were considered for pooling. Where several datasets were reported for the same population, only one dataset was included in further analyses in order to prevent duplication of participants. Datasets that most closely resembled the group of studies as a whole were selected: for two studies that looked at more than one definition of haematuria on microscopy, datasets that used a cut-off at 3–5 erythrocytes per hpf were selected.[56,59] One dataset was selected where the dipstick was read visually (rather than by photometry),[58] one was selected where a 'trace' dipstick result was regarded as positive[51] and one which used Multistix™ (Ames) was selected over another which used a less common test.[65]

Sensitivity ranged from 56% (specificity 89%) to 100% (specificity 18%, 64%). Specificity ranged from 18% (sensitivity 100%) to 99% (sensitivity 91%). Positive LRs ranged from 1.22 (LR– = 0.03) to 100 (LR– = 0.09). Negative LRs ranged from 0.01 (LR+ = 2.75) to 0.5 (LR+ = 5.06). The pooled LR+ was 5.99 [95% confidence interval (CI): 4.04 to 8.89] and the pooled LR– was 0.21 (95% CI: 0.17 to 0.26). These should be interpreted with extreme caution owing to the presence of significant heterogeneity ($p < 0.001$). *Figure 2* shows estimates of sensitivity and 1 – specificity plotted in receiver operating

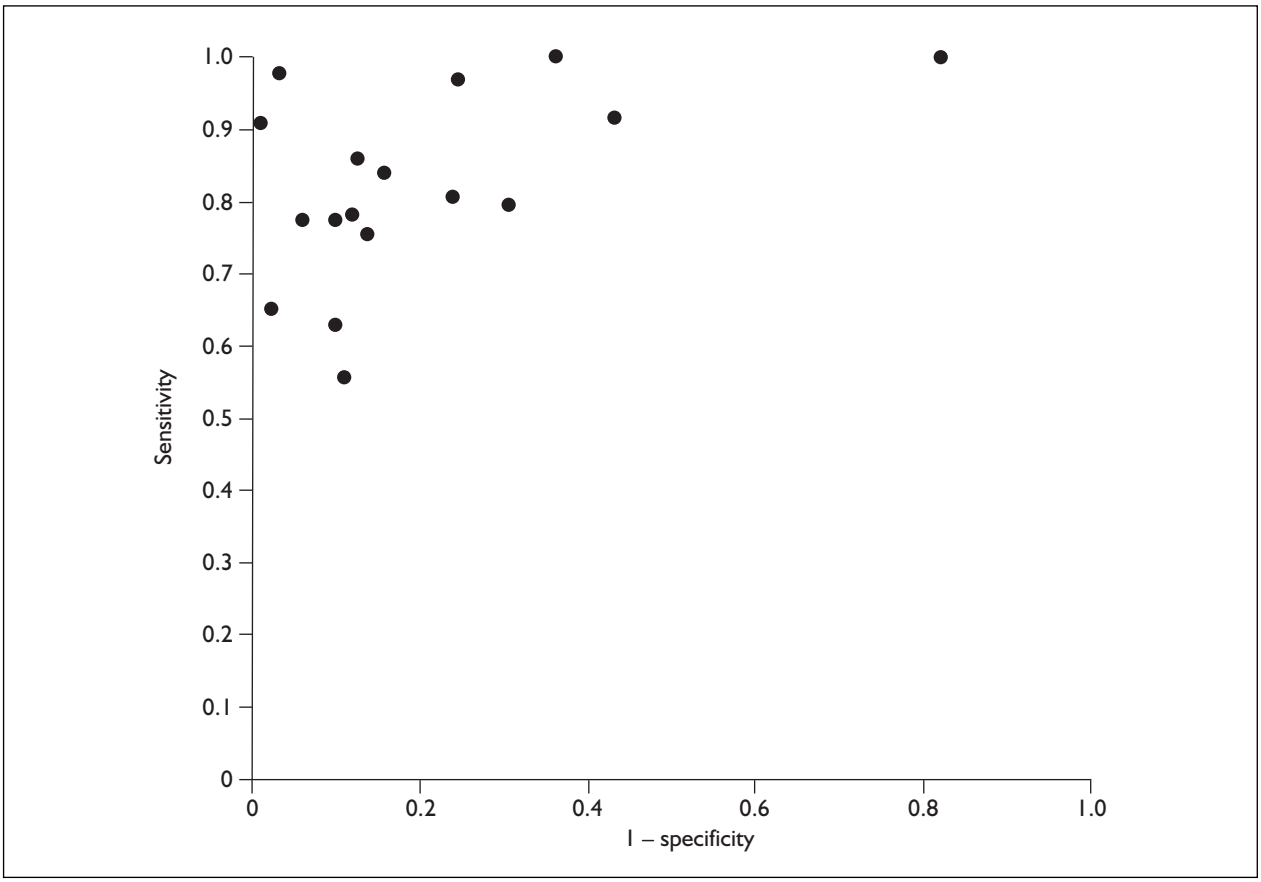


FIGURE 2 *Dipstick tests: study sensitivity and 1 – specificity plotted in ROC space*

TABLE 8 *QUADAS evaluation for studies of tests for the diagnosis of haematuria*

Study details	Appropriate spectrum composition	Selection criteria described	Appropriate reference standard	Disease progression bias avoided	Partial verification bias avoided	Differential verification bias avoided	Incorporation bias avoided	Test execution details reported adequately	Reference execution details reported adequately	Test review bias avoided	Diagnostic review bias avoided	Clinical review bias avoided	Uninterpretable results reported	Withdrawals accounted for
Arm (1986)[49]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Not clear	Yes
Bonard (1986)[50]	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Not clear	Not clear	Yes	Yes
Braun (1975)[51]	Not clear	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Not clear	Not clear	Yes	Not clear
Demol (1980)[52]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Not clear	Not clear	Yes	Not clear
Froom (1987)[53]	No	Yes	Not clear	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Not clear	Not clear	Not clear	Yes
Gibson (1986)[54]	Not clear	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Not clear	Yes
Gleeson (1993)[55]	Yes	No	Yes	Not clear	Yes	Yes	Yes	Yes	No	Not clear	Not clear	Yes	Not clear	Yes
Grinstead (1987)[56]	Not clear	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Not clear	Not clear	Yes	Yes
Gruhn (1974)[57]	No	No	Not clear	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Not clear	Not clear	Yes	Yes
Holland (1995)[58]	No	No	Yes	Not clear	Yes	Yes	Yes	Yes	Yes	Not clear	Not clear	Not clear	Not clear	Yes
Jaffe (1979)[59]	Not clear	Not clear	Yes	Not clear	Yes	Yes	Yes	Yes	Yes	Not clear	Not clear	Not clear	Yes	Not clear
Kutter (1974)[61]	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Not clear	Not clear	Yes	Yes
Kutter (1980)[60]	Not clear	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Not clear	Yes	Yes
McGlone (1990)[62]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Yes	Not clear	Yes
Messing (1987)[63]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Not clear	Yes	Not clear	Yes
Ooi (1998)[64]	No	Yes	Yes	Yes	Not clear	Yes	Yes	Yes	Yes	Yes	Not clear	Not clear	Not clear	Yes
Shaw (1985)[65]	Not clear	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Not clear	Yes	Yes	Yes
Wawroschek (1998)[66]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Not clear	Not clear	Yes	Yes
Yoo (1995)[67]	Not clear	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Not clear	Not clear	Not clear	Not clear

characteristic (ROC) space. The median LR+ was 5.58 (interquartile range: 3.39–7.91) and the median LR– was 0.24 (interquartile range 0.09–0.28).

A regression analysis was carried out to investigate possible explanations for the observed heterogeneity. The regression model $D = \alpha + \beta S$ was extended to include variables for methodological quality in the form of QUADAS items. Univariate regression analysis showed that the reporting of uninterpretable or indeterminate results was the only significant QUADAS variable. The DOR was around four times higher in studies that adequately reported uninterpretable and indeterminate results than in those that did not [RDOR 3.99 (95% CI: 1.22 to 13.10), $p = 0.03$].

Haematuria as a test for the presence of disease

Six studies (*Table 9*) used the presence of haematuria as a diagnostic test for urinary calculi[64,68,69,71] or bladder tumours.[70,72]

The definition of haematuria varied considerably between studies. Three studies defined haematuria by the number of RBCs/hpf on microscopy, and these studies reported thresholds of between any and 10 RBCs/hpf.[64,68,71] One study differentiated only between microhaematuria and macrohaematuria.[72] Of all the studies identified for this review, this was the only one that clearly presented data separately for macrohaematuria. The remaining studies reported only the presence of haematuria, without making the distinction whether this referred to macrohaematuria or microhaematuria.[69,70]

None of the studies used an appropriate spectrum of patients who would receive the test in practice. All studies using the presence of haematuria as a test to detect urinary calculi described the patient selection criteria. All but one study[68] avoided differential verification bias by ensuring that all patients received the same reference standard regardless of the index test result. All but one study[72] avoided incorporation bias (unclear) as the index test was independent of the reference standard and not part of it. For most studies it was unclear whether diagnostic review and clinical review bias had been avoided (with one exception[72]): whether the examiners were blind for the results of the index test when interpreting the reference standard and whether the same clinical data were available as when using the test in practice was unclear from the publications.

Four studies evaluated haematuria as test for urinary calculi.[64,68,69,71] Sensitivity ranged from 67% (specificity 66%, haematuria defined as >5 RBCs/hpf) to 95% (specificity 9–48%, haematuria defined as dipstick haematuria or ≥1 RBC). Specificity ranged from 9% (sensitivity 95%) to 66% (sensitivity 67%). LR+ ranged from 1.0 (LR– 0.5) to 2.0 (LR– 0.9) and LR– ranged from 0.1 (LR+ 1.8) to 0.6 (LR+ 1.4).

There was evidence for statistical heterogeneity in the LR+ ($p < 0.001$) and the LR– values ($p = 0.07$). The pooled estimate for the LR+ was 1.241 (95% CI: 1.039 to 1.482) and that for LR– was 0.296 (95% CI: 0.151 to 0.582), but especially the former value has to be interpreted with caution owing to the identified heterogeneity. For the pooling only one dataset for each study was used (restricting it to haematuria definitions >1 RBC/hpf or positive dipstick, dipstick haematuria, 2 RBCs/hpf on two occasions and the presence of microhaematuria).

A regression analysis was carried out to investigate possible sources for the observed heterogeneity in the four studies investigating urinary calculi. The regression model $D = \alpha + \beta S$ was extended to include the QUADAS items. Univariate regression analysis showed that the avoidance of differential verification bias was the only methodological quality variable that influenced the diagnostic results significantly. There was a tendency for a higher DOR in studies that avoided differential verification bias than in a study where it was unclear whether this bias had been avoided [relative diagnostic odds ratio (RDOR) 7.80 (95% CI: 2.46 to 24.76), $p = 0.0282$]. QUADAS results are given in *Table 10*.

The presence of haematuria as a test for bladder tumour was analysed in two studies showing a sensitivity of 93% (specificity 52%) in one study[70] and 62% (specificity 78%) in the other.[72] Although clinical experience suggests that macrohaematuria is frequently associated with malignancy, only one study that attempted to measure this association was identified.[72] When macrohaematuria alone was used as an indicator for bladder cancer, the sensitivity dropped to 10% and the specificity increased to 99%.[72] The LR+ ranged from 1.9 to 2.9 for microhaematuria and the LR– from 0.14 to 0.48. The values for macrohaematuria were 8.7 (LR– 0.91). The pooled LR+ was 2.31 (95% CI: 1.402 to 3.813) and the pooled LR– was 0.30 (95% CI: 0.085 to 1.084) when using the presence of

TABLE 9 *Haematuria as a test for the presence of disease*

Study details	Index test	Reference standard	TP	FP	FN	TN	Sensitivity	Specificity	LR+	LR–	DOR
Bove (1999)[68]	>1 RBC/hpf or positive dipstick	Unenhanced helical CT (presence of utererolithiasis)	82	71	13	29	86.3	29.0	1.2	0.47	2.6
	Any RBCs	Unenhanced helical CT (presence of utererolithiasis)	85	71	10	29	89.5	29.0	1.3	0.36	3.5
	>1 RBC/hpf)	Unenhanced helical CT (presence of utererolithiasis)	77	51	18	49	81.1	49.0	1.6	0.39	4.1
	>5 RBCs/hpf	Unenhanced helical CT (presence of utererolithiasis)	64	34	31	66	67.4	66.0	2.0	0.49	4.0
	Positive dipstick	Unenhanced helical CT (presence of utererolithiasis)	70	60	17	33	80.5	35.5	1.2	0.55	2.3
Freeland (1987)[69]	Dipstick haematuria (non-haemolysed trace to 3+)	IVU and visual examination of urine (urinary calculi present)	72	30	4	28	94.7	48.3	1.8	0.11	16.8
Ooi (1998)[64]	>5 RBCs/hpf for males, >10 RBCs/hpf for females	KUB and IVU, or calculi passed (urinary calculi present)	46	23	19	23	70.8	50.0	1.4	0.58	2.4
	Dipstick haematuria (≥1 RBC)	KUB and IVU, or calculi passed (urinary calculi present)	62	42	3	4	95.4	8.7	1.0	0.53	2.0
Safriel (2003)[71]	≥2 RBCs/hpf (on 2 occasions)	CT (urinary calculi present)	151	97	8	21	95.0	17.8	1.2	0.28	4.1
Parekattil (2003)[70]	Presence of haematuria	Cystoscopy (presence of bladder tumour)	25	109	2	117	92.6	51.8	1.9	0.14	13.4
Sanchez Carbayo (2000)[72]	Macrohaematuria (presence of macrohaematuria)	Cystoscopy (presence of bladder tumour)	6	2	55	174	9.8	98.9	8.7	0.91	9.5
	Microhaematuria (presence of microhaematuria)	Cystoscopy (presence of bladder tumour)	38	38	23	138	62.3	78.4	2.9	0.48	6.0

TABLE 10 *QUADAS evaluation for studies of haematuria as a test for benign or malignant lesions*

Study details	Appropriate spectrum composition	Selection criteria described	Appropriate reference standard	Disease progression bias avoided	Partial verification bias avoided	Differential verification bias avoided	Incorporation bias avoided	Test execution details reported adequately	Reference execution details reported adequately	Test review bias avoided	Diagnostic review bias avoided	Clinical review bias avoided	Uninterpretable results reported	Withdrawals accounted for
Bove (1999)[68]	No	Yes	Yes	Not clear	Yes	Not clear	Yes	Not clear	No	Not clear	Not clear	Not clear	Not clear	Not clear
Freeland (1987)[69]	No	Yes	Not clear	Yes	Yes	Yes	Yes	Yes	No	Yes	Not clear	Not clear	Not clear	Yes
Ooi (1998)[64]	No	Yes	Yes	Yes	Not clear	Yes	Yes	Yes	Yes	Yes	Not clear	Not clear	Not clear	Yes
Safriel (2003)[71]	No	Yes	Yes	Not clear	Yes	Yes	Yes	No	Yes	Not clear	Not clear	Not clear	Yes	Yes
Parekattil (2003)[70]	No	No	Yes	Not clear	Yes	Yes	Yes	No	No	Not clear	Not clear	Not clear	Not clear	Not clear
Sanchez Carbayo (2000)[72]	No	Not clear	Yes	Yes	Not clear	Yes	Not clear	Yes	Not clear	Not clear	Yes	Yes	Yes	Yes

microhaematuria as an indicator for bladder cancer. There was evidence for heterogeneity for the pooled LR+ and LR– ($p < 0.009$, $p < 0.058$), so the pooled values have to be interpreted with caution.

Further investigation to determine the underlying cause of haematuria

Eighty studies, reporting 192 data sets, investigated the diagnostic accuracy of tests to identify the underlying cause of haematuria. Studies in this category can be classified according to their clinical objective or target pathology.

Localisation of the source of bleeding

Forty-eight of the identified studies evaluated the accuracy of tests to localise the source of haematuria.[21,73–119]

These studies met between two and 13 of the 14 QUADAS validity criteria, with the median number of criteria met being seven (*Table 11*). In the majority of studies (43/48), partial verification could be seen to be avoided (it was reported that all participants received verification using the reference standard). Most studies also provided descriptions of how the index test was conducted (41/48), stated that the same reference standard was used regardless of the index test result (39/48) and explained withdrawals from the study (39/48). However, only one study reported attempts to avoid clinical review bias,[77] and very few described the execution of the reference standard (8/48) or gave any indication of the time elapsed between the index test and reference standard (6/48).

Studies in this section evaluated non-invasive tests. The methods used examined the morphology or volume distribution of erythrocytes present in the urine of patients with haematuria, in order to determine the most appropriate direction of further investigation for these patients. These approaches are based on the notion that glomerular bleeding is distinctive due to the presence of a large proportion of dysmorphic RBCs in the urine, in contrast to bleeding from lower in the urinary tract that is made up largely of isomorphic RBCs.[78,89] Similarly, it is thought that glomerular and lower tract bleeding result in distinct and different RBC volume distribution curves (RDCs). Two main approaches to the classification of haematuria were undertaken amongst these studies: single threshold and dual threshold. Single threshold studies gave a single cut-off for the proportion of RBCs in the urine that were dysmorphic (e.g. 80%), above which patients were considered to have haematuria of glomerular origin and below which they were diagnosed with non-glomerular haematuria, or described a single volume-related threshold. Some single threshold studies compared a range of cut-off values and their impact on diagnostic accuracy. Dual threshold studies each provided two cut-offs for the proportion of dysmorphic cells present in the urine (e.g. 20 and 80%); non-glomerular haematuria is diagnosed where the proportion of dysmorphic RBCs is less than the lower cut-off (20%) and glomerular haematuria where it is above the upper cut-off (80%). If the urine contains a proportion of dysmorphic cells that lies between the cut-off values (e.g. 20–80%), either no diagnosis or a 'mixed' diagnosis is made. Dual threshold studies assessing urinary RBC volume described volume-related thresholds for glomerular, lower tract and 'mixed' bleeding.

Data were extracted for all the cut-off values reported in both single and dual threshold localisation studies (see *Tables 12–15*). To allow pooling of data across these studies, 2×2 data from dual threshold studies were restructured as single threshold data. This involved the removal of the lower cut-off value and combining the original non-glomerular and 'mixed diagnosis' haematuria groups. The restructured dual threshold studies are therefore essentially single threshold studies that have dichotomised between the sources of bleeding on the basis of a single cut-off, above which the diagnosis is glomerular haematuria. The rationales for selecting the upper cut-off point (and thereby focusing on accurately diagnosing glomerular haematuria) were that the majority of single threshold studies were orientated in this manner and that the potential for a non-invasive test to detect glomerular bleeding accurately very early in the diagnostic pathway might impact on referral patterns to secondary care and/or prevent unnecessary investigation of the lower urinary tract. Where single threshold studies reported a series of cut-offs for the same set of patients, the one nearest the most commonly used cut-off for the whole group of studies (80%) was used. One study reported two datasets, one of which was a diagnostic cohort design and the other a case–control design.[118] The cohort was included owing to its stronger design. Studies were grouped by the diagnostic technique being evaluated. There were three main methods: light microscopy, phase contrast microscopy and automated volume analysis (flow cytometry).

TABLE 11 *QUADAS evaluation for studies of localisation of bleeding source in patients with haematuria*

Study details	Spectrum composition	Selection criteria	Appropriate reference standard	Disease progression bias	Partial verification bias	Differential verification bias	Incorporation bias	Test execution details	Reference execution details	Test review bias	Diagnostic review bias	Clinical review bias	Uninterpretable results	Withdrawals
Ahmad (1993)[73]	Yes	Yes	Yes	Not clear	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes
Andreev (1995)[74]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Yes	No
Apeland (2001)[75]	No	Yes	Not clear	Not clear	Yes	Yes	Yes	Yes	No	Yes	Yes	Not clear	Yes	Yes
Apeland (1995)[76]	No	No	Not clear	Not clear	Yes	Not clear	Not clear	Yes	No	Yes	Not clear	No	Yes	Yes
Banks (1989)[77]	Yes	Yes	Yes	Not clear	Yes	Yes	Yes	Yes	Yes	Not clear	Yes	Yes	Yes	Yes
Birch (1983)[78]	Yes	Yes	Not clear	Not clear	Not clear	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes
de Caestecker (1992)[79]	No	Yes	Not clear	Not clear	Yes	Not clear	Yes	Yes	No	Not clear	Yes	Not clear	Yes	Yes
Catala Lopez (2002)[80]	Yes	No	Not clear	Not clear	Yes	Yes	Yes	Yes	No	Yes	Not clear	Not clear	Not clear	Yes
Chu (1990)[81]	No	No	Yes	Not clear	Yes	Yes	Yes	Yes	No	Not clear	Yes	Not clear	Yes	Yes
Costa (1996)[82]	No	No	Not clear	Not clear	Not clear	Not clear	Yes	Yes	No	Yes	Not clear	Not clear	Yes	Yes
de Kermerchou (1993)[83]	Yes	Yes	Not clear	Not clear	Yes	Not clear	Not clear	Not clear	No	Not clear	Not clear	Not clear	Not clear	Yes
de Metz (1991)[84]	No	No	Not clear	Not clear	Yes	Yes	Yes	Yes	No	Yes	Yes	Not clear	Yes	Yes
De Santo (1987)[85]	Yes	No	Not clear	Not clear	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Not clear	Not clear
Docci (1988)[87]	Yes	Yes	Not clear	Not clear	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Not clear	Yes
Docci (1990)[86]	No	Yes	Not clear	Not clear	Yes	Yes	Yes	Yes	No	Not clear	Yes	Not clear	Yes	Yes
Eardley (2004)[88]	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Not clear	Not clear	Not clear	Yes	Yes
Fairley (1982)[89]	Yes	No	Not clear	Not clear	Yes	Not clear	Yes	Yes	Not clear	Not clear	Not clear	Not clear	Yes	Not clear
Fassett (1982)[90]	Yes	Yes	Not clear	Not clear	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes
Fünfstück (1989)[91]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Yes	Yes
Fukuzaki (1996)[92]	Yes	No	Yes	Not clear	No	Yes	Yes	Yes	No	Yes	Not clear	Not clear	Yes	No
Game (2003)[93]	Yes	Yes	Yes	Not clear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Yes	Yes
Gerc (1997)[94]	Yes	Not clear	Not clear	Not clear	Not clear	Yes	Not clear	Yes	No	Not clear	Not clear	Not clear	No	Yes
Gimbel (1988)[95]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Yes	Yes
Goncalves (1986)[96]	No	Not clear	Yes	Not clear	Yes	Not clear	Not clear	Yes	No	Not clear	Not clear	Not clear	Yes	Yes
Hirakawa (1995)[98]	Yes	No	Not clear	Not clear	Yes	Not clear	Not clear	Yes	No	Not clear	Not clear	Not clear	No	Yes
Hirakawa (1994)[97]	Yes	Yes	Not clear	Not clear	Yes	Not clear	Not clear	Yes	No	Not clear	Not clear	Not clear	Not clear	Yes
Hyodo (1995)[101]	Yes	No	No	Not clear	Yes	Yes	Yes	Yes	No	Yes	Not clear	Not clear	Not clear	Yes
Hyodo (1999)[100]	Yes	Yes	Yes	Not clear	Yes	Yes	Yes	No	No	Not clear	Not clear	Not clear	Not clear	Yes
Hyodo (1997)[99]	Not clear	No	Yes	Not clear	Yes	Yes	Yes	No	No	Not clear	Not clear	Not clear	Yes	Yes
Janssens (1992)[102]	No	No	Not clear	Not clear	Not clear	Yes	Not clear	Yes	No	Not clear	Not clear	Not clear	No	No
Jean (1993)[103]	Yes	No	Not clear	Not clear	Yes	Yes	Yes	Yes	No	Not clear	Not clear	Not clear	Yes	Yes

continued

TABLE 11 *QUADAS evaluation for studies of localisation of bleeding source in patients with haematuria (cont'd)*

Study details	Spectrum composition	Selection criteria	Appropriate reference standard	Disease progression bias	Partial verification bias	Differential verification bias	Incorporation bias	Test execution details	Reference execution details	Test review bias	Diagnostic review bias	Clinical review bias	Uninterpretable results	Withdrawals
Kohler (1991)[104]	Yes	No	Yes	Not clear	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Not clear	Not clear	Not clear
Kore (1999)[21]	No	No	Not clear	Not clear	Yes	Yes	Yes	Yes	No	Not clear	Yes	Not clear	Yes	Yes
Liu (1986)[105]	Not clear	No	Not clear	Not clear	Yes	Yes	Not clear	Yes	No	Yes	Yes	Not clear	Yes	Yes
Mohammad (1993)[106]	Yes	No	Yes	Not clear	No	No	Yes	Yes	No	Not clear	Not clear	Not clear	Yes	0
Nagy (1985)[107]	Yes	No	Not clear	Not clear	Yes	Not clear	Yes	No	No	Not clear	Yes	Not clear	Yes	Yes
Naicker (1992)[108]	No	No	Not clear	Not clear	Yes	Yes	Yes	Yes	No	Yes	Yes	Not clear	Yes	Yes
Obronieka (1998)[109]	Yes	Yes	Not clear	Not clear	Yes	Yes	Yes	Yes	No	Not clear	Not clear	Not clear	Yes	Yes
Rath (1991)[110]	Yes	No	Not clear	Not clear	Yes	Not clear	Yes	Yes	No	Yes	Yes	Not clear	Yes	Yes
Roth (1991)[111]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Yes	Yes
Saito (1999)[112]	No	No	Not clear	Not clear	Yes	Yes	Yes	Yes	No	Not clear	Yes	Not clear	Yes	Not clear
Sayer (1990)[113]	Yes	No	Yes	Not clear	Yes	Yes	Yes	Yes	No	Not clear	Yes	Not clear	Yes	Yes
Shichiri (1988)[114]	Yes	Yes	Not clear	Not clear	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes
Singbal (1996)[115]	Yes	No	Not clear	Not clear	Yes	Yes	Yes	Yes	No	Yes	Yes	Not clear	Not clear	Yes
Tomita (1992)[116]	No	No	Not clear	Not clear	Yes	Yes	Yes	Yes	No	Not clear	Yes	Not clear	Yes	Yes
Uhl (1995)[117]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Not clear	Not clear	Not clear	Yes	Yes
Wankowicz (1991)[118]	Yes	Yes	Not clear	Not clear	Yes	Yes	Not clear	Yes	No	Not clear	Not clear	Not clear	Yes	Yes
Wann (1986)[119]	Yes	No	Not clear	Not clear	Yes	Not clear	Yes	No	No	Not clear	Not clear	Not clear	Yes	Not clear

TABLE 12 *Results of studies of light microscopy for the localisation of bleeding in patients with haematuria*

Study details	Index test (definition of a +ve test)	Reference test (definition of a +ve test)	TP	FP	FN	TN	Sensitivity	Specificity	LR+	LR–	DOR
Single threshold											
Apeland (2001)[75]	Bright-field, using Sternheimer–Malbin stain (glomerular)	Previously established diagnosis (established glomerular disease)	28	10	3	38	90.3	79.2	4.3	0.12	35.5
Costa (1996)[82]	Glomerular: >40% dysmorphic RBCs	Final diagnosis (haematuria of glomerular origin)	22	3	0	14	100.0	82.4	5.7	0.00	NC
	Glomerular: >50% dysmorphic RBCs	Final diagnosis (haematuria of glomerular origin)	22	1	0	16	100.0	94.1	17.0	0.00	NC
	Glomerular: >60% dysmorphic RBCs	Final diagnosis (haematuria of glomerular origin)	22	1	0	16	100.0	94.1	17.0	0.00	NC
	Glomerular: >80% dysmorphic RBCs	Final diagnosis (haematuria of glomerular origin)	16	0	6	17	72.7	100.0	NC	0.27	NC
	Glomerular: >1% dysmorphic RBCs	Final diagnosis (haematuria of glomerular origin)	22	17	0	0	100.0	0.0	1.0	NC	NC
	Glomerular: >20% dysmorphic RBCs	Final diagnosis (haematuria of glomerular origin.)	22	11	0	6	100.0	35.3	1.5	0.00	NC
	Glomerular: >10% dysmorphic RBCs	Final diagnosis (haematuria of glomerular origin)	22	14	0	3	100.0	17.6	1.2	0.00	NC
	Glomerular: >90% dysmorphic RBCs	Final diagnosis (haematuria of glomerular origin)	4	0	18	17	18.2	100.0	NC	0.82	NC
	Glomerular: >30% dysmorphic RBCs	Final diagnosis (haematuria of glomerular origin)	22	8	0	9	100.0	52.9	2.1	0.00	NC
	Glomerular: >70% dysmorphic RBCs	Final diagnosis (haematuria of glomerular origin)	20	0	2	17	90.9	100.0	NC	0.09	NC
Fukuzaki (1996)[92]	Immunocytochemical staining	Final diagnosis (diagnosis of a renal disorder)	23	3	0	15	100.0	83.3	6.0	0.00	NC
Janssens (1992)[102]	Immunocytochemical staining (glomerular: ≥60% coloured cells)	Previously established diagnosis (diagnosis certain to be renal or non-renal based on clinical assessment)	26	0	0	27	100.0	100.0	NC	0.00	NC
	Urinary RBC morphology (glomerular: 50% dysmorphic RBCs)	Previously established diagnosis (diagnosis certain to be renal or non-renal based on clinical assessment)	22	3	4	18	84.6	85.7	5.9	0.18	33.0

continued

TABLE 12 *Results of studies of light microscopy for the localisation of bleeding in patients with haematuria (cont'd)*

Study details	Index test (definition of a +ve test)	Reference test (definition of a +ve test)	TP	FP	FN	TN	Sensitivity	Specificity	LR+	LR–	DOR
	Urinary RBC morphology (glomerular: 70% dysmorphic RBCs)	Previously established diagnosis (diagnosis certain to be renal or non-renal based on clinical assessment)	14	0	12	21	53.8	100.0	NC	0.46	NC
	Urinary RBC morphology (glomerular: 40% dysmorphic RBCs)	Previously established diagnosis (diagnosis certain to be renal or non-renal based on clinical assessment)	24	4	2	17	92.3	81.0	4.8	0.10	51.0
	Urinary RBC morphology (glomerular: 30% dysmorphic RBCs)	Previously established diagnosis (diagnosis certain to be renal or non-renal based on clinical assessment)	25	6	1	15	96.2	71.4	3.4	0.05	62.5
	Urinary RBC morphology (glomerular: 60% dysmorphic RBCs)	Previously established diagnosis (diagnosis certain to be renal or non-renal based on clinical assessment)	19	1	7	20	73.1	95.2	15.3	0.28	54.3
Lui (1986)[105]	Benzidine dye used (glomerular: majority RBCs dysmorphic)	Previously established diagnosis (diagnosis of glomerular disease)	33	1	3	30	91.7	96.8	28.4	0.09	330.0
Saito (1999)[112]	Urinary RBC morphology (glomerular: >80% dysmorphic RBCs)	Previously established diagnosis	11	1	58	33	15.9	97.1	5.4	0.87	6.3
	Urinary RBC morphology (glomerular: >30% dysmorphic RBCs)	Previously established diagnosis	60	5	9	29	87.0	85.3	5.9	0.15	38.7
	Urinary RBC morphology (glomerular: >20% dysmorphic RBCs)	Previously established diagnosis	65	10	4	24	94.2	70.6	3.2	0.08	39.0
	Urinary RBC morphology (glomerular: >90% dysmorphic RBCs)	Previously established diagnosis	6	0	63	34	8.7	100.0	NC	0.91	NC
	Urinary RBC morphology (glomerular: >40% dysmorphic RBCs)	Previously established diagnosis	56	4	13	30	81.2	88.2	6.9	0.21	32.3

continued

TABLE 12 *Results of studies of light microscopy for the localisation of bleeding in patients with haematuria (cont'd)*

Study details	Index test (definition of a +ve test)	Reference test (definition of a +ve test)	TP	FP	FN	TN	Sensitivity	Specificity	LR+	LR–	DOR
	Urinary RBC morphology (glomerular: >50% dysmorphic RBCs)	Previously established diagnosis	48	2	21	32	69.6	94.1	11.8	0.32	36.6
	Urinary RBC morphology (glomerular: >60% dysmorphic RBCs)	Previously established diagnosis	36	2	33	32	52.2	94.1	8.9	0.51	17.5
	Urinary RBC morphology (glomerular: >10% dysmorphic RBCs)	Previously established diagnosis	67	17	2	17	97.1	50.0	1.9	0.06	33.5
	Urinary RBC morphology (glomerular: >70% dysmorphic RBCs)	Previously established diagnosis	24	1	45	33	34.8	97.1	11.8	0.67	17.6
Singbal (1996)[115]	Light microscopy (glomerular: >20% dysmorphic RBCs)	Final diagnosis (diagnosis of glomerular haematuria; diagnoses included minimal change nephrotic syndrome with mild mesangial matrix increase, acute glomerulonephritis, focal proliferative glomerulonephritis, chronic glomerulonephritis, crescentic glomerulonephritis, mesangioproliferative glomerulonephritis, membranous glomerulonephritis, systemic lupus erythromatosus)	28	3	2	47	93.3	94.0	15.6	0.07	219.3
Uhl (1995)[117]	(Glomerular: ≥30% deformed RBCs)	Previously established diagnosis (positive, clinical diagnosis = glomeral disease, negative, clinical diagnosis = non-glomeral disease)	78	8	13	88	85.7	91.7	10.3	0.16	66.0

continued

TABLE 12 *Results of studies of light microscopy for the localisation of bleeding in patients with haematuria (cont'd)*

Study details	Index test (definition of a +ve test)	Reference test (definition of a +ve test)	TP	FP	FN	TN	Sensitivity	Specificity	LR+	LR–	DOR
Dual threshold											
Chu (1990)[81]	Wright's stain used (non-glomerular: <10% of RBCs with glomerular morphology. Glomerular and mixed classified as negative)	Previously established diagnosis (haematuria of non-glomerular origin)	17	1	0	17	100.0	94.4	18.0	0.00	NC
	Wright's stain used (glomerular: >20% of RBCs with glomerular morphology. Non-glomerular and mixed classified as negative)	Previously established diagnosis (haematuria of glomerular origin)	14	0	4	17	77.8	100.0	NC	0.22	NC
	Wright's stain used (glomerular: >80% of RBCs distorted with variation in size and shape, and fragmentation. Non-glomerular and mixed are classified as negative)	Previously established diagnosis (haematuria of glomerular origin)	11	0	7	17	61.1	100.0	NC	0.39	NC
	Wright's stain used (non-glomerular: >80% of RBCs undistorted and uniform in size and shape. Glomerular and mixed classified as negative)	Previously established diagnosis (haematuria of non-glomerular origin)	17	5	0	13	100.0	72.2	3.6	0.00	NC
de Metz (1991)[84]	Light microscopy, using May–Grunwald–Giemsa stain (non-glomerular: ≥ 80% isomorphic RBCs. Glomerular and mixed are classified as negative)	Previously established diagnosis (non-renal haematuria)	15	0	18	28	45.5	100.0	NC	0.55	NC

continued

TABLE 12 *Results of studies of light microscopy for the localisation of bleeding in patients with haematuria (cont'd)*

Study details	Index test (definition of a +ve test)	Reference test (definition of a +ve test)	TP	FP	FN	TN	Sensitivity	Specificity	LR+	LR–	DOR
	Light microscopy, using May–Grunwald–Giemsa stain (glomerular: ≥80% dysmorphic RBCs. Non-glomerular and mixed are classified as negative)	Previously established diagnosis (renal haematuria)	22	2	6	31	78.6	93.9	13.0	0.23	56.8
Fünfstück (1989)[91]	Erythrocyte morphology, urine sediment analysis (non-glomerular: <20% dysmorphic RBCs. Glomerular and mixed classified as negative)	Previously established diagnosis (clinical diagnosis of non-renal haematuria)	69	0	6	135	92.0	100.0	NC	0.08	NC
	Erythrocyte morphology, urine sediment analysis (glomerular: >70% dysmorphic RBCs. Non-glomerular and mixed classified as negative)	Previously established diagnosis (clinical diagnosis of glomerulonephritis)	128	0	7	75	94.8	100.0	NC	0.05	NC
Nagy (1985)[107]	Urinary RBC morphology [glomerular: >70% of RBCs showing abnormalities, being small, irregularly shaped and deformed. Non-glomerular and mixed (intact and altered RBCs in equal proportion) are defined as negative]	Previously established diagnosis (abnormality that accounts for the haematuria)	115	0	5	80	95.8	100.0	NC	0.04	NC
	Urinary RBC morphology [non-glomerular: sediment contained intact, regularly round RBCs of uniform size. Glomerular and mixed (intact and altered RBCs in equal proportion) are defined as negative]	Previously established diagnosis (abnormality that accounts for the haematuria)	80	5	0	115	100.0	95.8	24.0	0.00	NC

continued

TABLE 12 *Results of studies of light microscopy for the localisation of bleeding in patients with haematuria (cont'd)*

Study details	Index test (definition of a +ve test)	Reference test (definition of a +ve test)	TP	FP	FN	TN	Sensitivity	Specificity	LR+	LR–	DOR
Rath (1991)[110]	Bright field microscopy (non-glomerular: <20% dysmorphic RBCs. Glomerular and mixed are classified as negative)	Previously established diagnosis (established diagnosis of non-glomerular haematuria)	20	14	2	86	90.9	86.0	6.5	0.11	61.4
	Bright field microscopy (glomerular: >80% dysmorphic RBCs. Non-glomerular and mixed are classified as negative)	Previously established diagnosis (established diagnosis of glomerular disease)	60	1	40	21	60.0	95.5	13.2	0.42	31.5

NC, not calculated, zero denominator.

TABLE 13 *Results of studies of phase contrast microscopy for the localisation of bleeding in patients with haematuria*

Study details	Index test (definition of a +ve test)	Reference test (definition of a +ve test)	TP	FP	FN	TN	Sensitivity	Specificity	LR+	LR–	DOR
Single threshold											
Andreev (1995)[74]	PCM, urinary RBC morphology (glomerular: ≥15% of dysmorphic RBCs)	Previously established diagnosis (diagnosis of glomerular disease)	39	2	3	18	92.9	90.0	9.3	0.08	117.0
Birch (1983)[78]	PCM, urinary RBC morphology (glomerular: dysmorphic changes in RBCs Non-glomerular defined as negative: RBCs morphologically normal, with not more than 2 cell populations present)	Final diagnosis (not reported)	86	2	1	28	98.9	93.3	14.8	0.01	1204.0
Catala Lopez (2002)[80]	PCM, acanthocyte count (glomerular haematuria: ≥5% acanthocytes)	Previously established diagnosis (glomerular disease as clinical diagnosis)	64	0	9	97	87.7	100.0	NC	0.12	NC
	PCM, urinary RBC morphology (glomerular haematuria: ≥35% dysmorphic RBCs)	Previously established diagnosis (glomerular disease as clinical diagnosis)	50	0	23	97	68.5	100.0	NC	0.32	NC
de Kermerchou (1993)[83]	PCM (glomerular: >15 dysmorphic RBCs per mm^3 of urine)	Previously established diagnosis [haematuria of nephrological (rather than urological) origin]	48	22	8	6	85.7	21.4	1.1	0.67	1.6
	PCM (glomerular: >80 dysmorphic RBCs per mm^3 of urine)	Previously established diagnosis [haematuria of nephrological (rather than urological) origin]	2	1	54	27	3.6	96.4	1.0	1.00	1.0
	PCM (glomerular: >20 dysmorphic RBCs per mm^3 of urine)	Previously established diagnosis [haematuria of nephrological (rather than urological) origin]	41	11	15	17	73.2	60.7	1.9	0.44	4.2

continued

TABLE 13 *Results of studies of phase contrast microscopy for the localisation of bleeding in patients with haematuria (cont'd)*

Study details	Index test (definition of a +ve test)	Reference test (definition of a +ve test)	TP	FP	FN	TN	Sensitivity	Specificity	LR+	LR–	DOR
	PCM (glomerular: >10 dysmorphic RBCs per mm^3 of urine)	Previously established diagnosis [haematuria of nephrological (rather than urological) origin]	52	23	4	5	92.9	17.9	1.1	0.40	2.8
Fairley (1982)[89]	PCM (glomerular: dysmorphic RBCs present)	Final diagnosis (not reported)	55	0	3	30	94.8	100.0	NC	0.05	NC
Gerc (1997)[94]	PCM (glomerular: ≥20% of RBCs characterised as being 'glomerular')	Previously established diagnosis [a nephrological (rather than urological) cause of haematuria]	19	6	18	23	51.4	79.3	2.5	0.61	4.0
	PCM (glomerular: ≥10% of RBCs characterised as being 'glomerular')	Previously established diagnosis [a nephrological (rather than urological) cause of haematuria]	25	10	12	19	67.6	65.5	2.0	0.50	4.0
	PCM (glomerular: ≥30% of RBCs characterised as being 'glomerular')	Previously established diagnosis [a nephrological (rather than urological) cause of haematuria]	10	3	27	26	27.0	89.7	2.6	0.81	3.2
Goncalves (1986)[96]	PCM (glomerular: ≥35% dysmorphic RBCs)	Final diagnosis (patients were categorised as with having haematuria of glomerular aetiology or non-glomerular aetiology)	44	3	2	44	95.7	93.6	15.0	0.05	322.7
Goncalves (1986)[96]	PCM (glomerular: ≥65% dysmorphic RBCs)	Final diagnosis (patients were categorised as with having haematuria of glomerular aetiology or non-glomerular aetiology)	40	0	6	47	87.0	100.0	NC	0.13	NC
	PCM (glomerular: ≥80% dysmorphic RBCs)	Final diagnosis (patients were categorised as with having haematuria of glomerular aetiology or non-glomerular aetiology)	30	0	16	47	65.2	100.0	NC	0.35	NC

continued

TABLE 13 *Results of studies of phase contrast microscopy for the localisation of bleeding in patients with haematuria (cont'd)*

Study details	Index test (definition of a +ve test)	Reference test (definition of a +ve test)	TP	FP	FN	TN	Sensitivity	Specificity	LR+	LR–	DOR
	PCM (glomerular: ≥20% dysmorphic RBCs)	Final diagnosis (patients were categorised as with having haematuria of glomerular aetiology or non-glomerular aetiology)	44	7	2	40	95.7	85.1	6.4	0.05	125.7
	PCM (glomerular: ≥50% dysmorphic RBCs)	Final diagnosis (patients were categorised as with having haematuria of glomerular aetiology or non-glomerular aetiology)	44	2	2	45	95.7	95.7	22.5	0.05	495.0
Lui (1986)[105]	PCM (glomerular: majority RBCs dysmorphic)	Previously established diagnosis (diagnosis of glomerular disease)	33	1	3	30	91.7	96.8	28.4	0.09	330.0
Mohammad (1993)[106]	PCM (glomerular: >20% dysmorphic RBCs)	Final diagnosis (histologically confirmed glomerulopathy)	27	3	0	17	100.0	85.0	6.7	0.00	NC
Naicker (1992)[108]	PCM, urinary RBC morphology (glomerular: >50% of RBCs dysmorphic)	Previously established diagnosis (established glomerular cause of haematuria)	13	12	7	6	65.0	33.3	1.0	1.05	0.9
Roth (1991)[111]	PCM (glomerular: >40% dysmorphic RBCs)	Previously established diagnosis (histologically confirmed glomerular disease)	10	0	0	20	100.0	100.0	NC	0.00	NC
Singbal (1996)[115]	PCM (glomerular: >20% dysmorphic RBCs)	Final diagnosis (acute glomerulonephritis diagnosed according to clinical and laboratory criteria. Other glomerulo-nephropathies were confirmed by renal biopsy)	29	3	1	47	96.7	94.0	16.1	0.04	454.3

continued

TABLE 13 *Results of studies of phase contrast microscopy for the localisation of bleeding in patients with haematuria (cont'd)*

Study details	Index test (definition of a +ve test)	Reference test (definition of a +ve test)	TP	FP	FN	TN	Sensitivity	Specificity	LR+	LR–	DOR
Dual threshold											
Ahmad (1993)[73]	PCM, urinary RBC morphology (glomerular: urinary RBCs showing a wide range of variation, frequently with loss of haemoglobin. Non-glomerular and mixed are classified as negative)	Final diagnosis (glomerulo-nephritis proven by renal biopsy)	58	1	4	42	93.5	97.7	40.2	0.07	609.0
	PCM, urinary RBC morphology (non-glomerular: RBCs morphologically uniform with not more than two cell populations present. Glomerular and mixed are classified as negative)	Final diagnosis (non-glomerular haematuria)	40	1	3	61	93.0	98.4	57.7	0.07	813.3
Chu (1990)[81]	PCM (non-glomerular: <10% of RBCs with glomerular morphology. Glomerular and mixed classified as negative)	Previously established diagnosis (haematuria of non-glomerular origin)	17	1	0	17	100.0	94.4	18.0	0.00	NC
	PCM (non-glomerular: >80% of RBCs undistorted and uniform in size and shape. Glomerular and mixed classified as negative)	Previously established diagnosis (haematuria of non-glomerular origin)	17	5	0	13	100.0	72.2	3.6	0.00	NC
	PCM (glomerular: >20% of RBCs with glomerular morphology. Non-glomerular and mixed classified as negative)	Previously established diagnosis (haematuria of glomerular origin)	13	0	5	17	72.2	100.0	NC	0.28	NC

continued

TABLE 13 *Results of studies of phase contrast microscopy for the localisation of bleeding in patients with haematuria (cont'd)*

Study details	Index test (definition of a +ve test)	Reference test (definition of a +ve test)	TP	FP	FN	TN	Sensitivity	Specificity	LR+	LR–	DOR
	PCM (glomerular: >80% of RBCs distorted with variation in size and shape, and fragmentation. Non-glomerular and mixed are classified as negative)	Previously established diagnosis (haematuria of glomerular origin)	11	0	7	17	61.1	100.0	NC	0.39	NC
de Metz (1991)[84]	PCM (glomerular: ≥80% dysmorphic RBCs. Non-glomerular and mixed are classified as negative)	Previously established diagnosis (renal haematuria)	24	1	3	32	88.9	97.0	29.3	0.11	256.0
	PCM (non-glomerular: ≥80% isomorphic RBCs. Glomerular and mixed are classified as negative)	Previously established diagnosis (non-renal haematuria)	16	0	17	27	48.5	100.0	NC	0.52	NC
De Santo (1987)[85]	PCM, urinary RBC morphology (glomerular: >80% dysmorphic RBCs on 2 non-consecutive days. Non-glomerular and mixed are classified as negative)	Final diagnosis	81	3	5	79	94.2	96.3	25.7	0.06	426.6
	PCM, urinary RBC morphology (non-glomerular: >80% uniform RBCs. Glomerular and mixed are classified as negative)	Final diagnosis	79	0	3	86	96.3	100.0	NC	0.04	NC
Fassett (1982)[90]	PCM (glomerular bleeding: > 80% urinary red cells distorted. Non-glomerular and mixed are classified as negative)	Final diagnosis	115	5	33	100	77.7	95.2	16.3	0.23	69.7

continued

TABLE 13 *Results of studies of phase contrast microscopy for the localisation of bleeding in patients with haematuria (cont'd)*

Study details	Index test (definition of a +ve test)	Reference test (definition of a +ve test)	TP	FP	FN	TN	Sensitivity	Specificity	LR+	LR–	DOR
	PCM (non-glomerular: > 80% urinary red cells undistorted. Glomerular and mixed are classified as negative)	Final diagnosis	100	5	7	141	93.5	96.6	27.3	0.07	402.9
Fukuzaki (1996)[92]	PCM (glomerular: >70% of red cells in the sediment were dysmorphic. Non-glomerular and mixed were defined as negative)	Final diagnosis (diagnosis of a renal disorder)	19	8	4	10	82.6	55.6	1.9	0.31	5.9
	PCM (non-glomerular: >70% of red cells were normal. Glomerular and mixed are defined as negative)	Final diagnosis (diagnosis of a non-renal disorder)	10	2	8	21	55.6	91.3	6.4	0.49	13.1
Game (2003)[93]	PCM (non-glomerular result. Glomerular and mixed results are defined as negative. Cut-off values not reported)	Final diagnosis (non-glomerular diagnosis)	7	0	5	16	58.3	100.0	NC	0.42	NC
	PCM (glomerular: non-glomerular and mixed results are defined as negative. Cut-off values not reported)	Final diagnosis (glomerular diagnosis)	10	2	6	10	62.5	83.3	3.8	0.45	8.3
Obroniecka (1998)[109]	PCM (glomerular: >60% dysmorphic RBCs. Non-glomerular and mixed are defined as negative)	Final diagnosis (diagnosis of glomerular disease)	54	3	8	3	87.1	50.0	1.7	0.26	6.8
	PCM (non-glomerular: <20% dysmorphic RBCs. Glomerular and mixed are defined as negative)	Final diagnosis (diagnosis of urological disease)	55	3	1	10	98.2	76.9	4.3	0.02	183.3

continued

TABLE 13 *Results of studies of phase contrast microscopy for the localisation of bleeding in patients with haematuria*

Study details	Index test (definition of a +ve test)	Reference test (definition of a +ve test)	TP	FP	FN	TN	Sensitivity	Specificity	LR+	LR–	DOR
Wankowicz (1991)[118]	Phase contrast microscopy (glomerular: >60% dysmorphic RBCs. Non-glomerular and mixed are classified as negative)	Final diagnosis (glomerulonephritis. Other renal and nephrological disorders were classed as negative)	2	0	6	15	25.0	100.0	NC	0.75	NC
	PCM (non-glomerular: ≤20% dysmorphic RBCs. Glomerular and mixed are classified as negative)	Previously established diagnosis (non-glomerular cause of bleeding)	13	0	0	5	100.0	100.0	NC	0.00	NC
	PCM (glomerular: >60% dysmorphic RBCs. Non-glomerular and mixed are classified as negative)	Previously established diagnosis (glomerulonephritis. Other renal and nephrological disorders were classed as negative)	4	0	1	13	80.0	100.0	NC	0.20	NC
	Phase contrast microscopy (non-glomerular: ≤ 20% dysmorphic RBCs. Glomerular and mixed are classed as negative)	Final diagnosis (non-glomerular cause of bleeding)	15	0	0	8	100.0	100.0	NC	0.00	NC
Wann (1986)[119]	Phase contrast microscopy, urinary RBC morphology (glomerular: ≥80% dysmorphic RBCs. Non-glomerular defined as negative: ≥80% isomorphic RBC)	Final diagnosis	48	5	0	35	100.0	87.5	8.0	0.00	NC

NC, not calculated, zero denominator.

TABLE 14 *Results of studies of automated analysis methods for the localisation of bleeding in patients with haematuria*

Study details	Index test (definition of a +ve test)	Reference test (definition of +ve test)	TP	FP	FN	TN	Sensitivity	Specificity	LR+	LR–	DOR
Single threshold studies											
Apeland (1995)[76]	Urinary RBC volume and density {glomerular: index value <1. The index value was defined as test index = [count area 1 – (RBC dil) – count area 1 (HGB dil)]/[count area 2 (RBC dil) – count area 2 (HGB dil)]}. HGB dil and RBC dil are reagents supplied by Technicon Chemicals, Belgium	Final diagnosis (glomerular cause of haematuria diagnosed)	37	5	6	15	86.0	75.0	3.4	0.19	18.5
Apeland (2001)[75]	Urinary RBC size [glomerular: >80% of RBC volumes ≤ 126 channels and <80% ≥84 channels. Additional criteria applied to mixed picture samples: presence of increased numbers of small round cells (i.e. mostly renal tubular cells) or pathological casts made renal bleeding more likely. Presence of high levels of leucocytes, bacteria or yeast indicated a non-glomerular disorder]	Previously established diagnosis (established glomerular disease)	29	8	2	40	93.5	83.3	5.6	0.08	72.5
Banks (1989)[77]	Urinary RBC volume (glomerular: mean corpuscular volume of urinary RBCs <80 fl)	Final diagnosis (diagnosis of a glomerular disease)	18	3	3	18	85.7	85.7	6.0	0.17	36.0
Docci (1988)[87]	Urinary RBC size (glomerular)	Final diagnosis (biopsy-proven glomerular disease)	15	1	0	38	100.0	97.4	39.0	0.00	NC
Docci (1990)[86]	Urinary RBC size [glomerular: mean cellular volume (MCV) <70 fl]	Final diagnosis (established glomerular disease)	29	5	2	49	93.5	90.7	10.1	0.07	142.1

continued

TABLE 14 *Results of studies of automated analysis methods for the localisation of bleeding in patients with haematuria (cont'd)*

Study details	Index test (definition of a +ve test)	Reference test (definition of +ve test)	TP	FP	FN	TN	Sensitivity	Specificity	LR+	LR–	DOR
Jean (1993)[103]	Urinary RBC volume (glomerular: volume >71 fl)	Previously established diagnosis (diagnosis of glomerular disease)	42	5	23	30	64.6	85.7	4.5	0.41	11.0
Jean (1993)[103]	Urinary RBC volume (glomerular: volume >71 fl)	Previously established diagnosis (diagnosis of glomerular disease)	40	0	22	1	64.5	100.0	NC	0.35	NC
Jean (1993)[103]	Urinary RBC volume (glomerular: volume >71 fl)	Previously established diagnosis (diagnosis of glomerular disease)	2	5	1	29	66.7	85.3	4.5	0.39	11.6
Kore (1999)[21]	Urinary RBC volume (Glomerular: mean cell size <4.75 μm)	Final diagnosis (Clinical diagnosis of glomerular disease)	18	2	2	47	90.0	95.9	22.1	0.10	211.5
Naicker (1992)[108]	Urinary RBC volume (glomerular: urinary RBC size distribution curve that peaked at a volume less than that of the peripheral RBCs. A mixed pattern was recorder if distinct glomerular and non-glomerular populations were present and the glomerular portion was >2% of the total. Treatment of mixed results is unclear)	Previously established diagnosis (established glomerular cause of haematuria)	19	1	1	17	95.0	94.4	17.1	0.05	323.0
Sayer (1990)[113]	Urinary RBC volume (glomerular: broad, uneven distribution curve reflecting the varying size and shapes of dysmorphic RBCs. Sharp, peaked curve representing a uniform, homogeneous population of RBCs indicating non-glomerular diseases classified as negative)	Previously established diagnosis (positive for glomerular disease)	52	0	0	48	100.0	100.0	NC	0.00	NC

continued

TABLE 14 *Results of studies of automated analysis methods for the localisation of bleeding in patients with haematuria (cont'd)*

Study details	Index test (definition of a +ve test)	Reference test (definition of +ve test)	TP	FP	FN	TN	Sensitivity	Specificity	LR+	LR–	DOR
Dual threshold studies											
de Caestecker (1992)[79]	Urinary RBC volume (non-glomerular: modal volume 60–180 fl, where modal volumes were derived from volume frequency histograms. Glomerular and mixed are classified as negative)	Previously established diagnosis (non-glomerular haematuria)	29	0	12	97	70.7	100.0	NC	0.29	NC
de Caestecker (1992)[79]	Urinary RBC volume (glomerular: modal volume 30–59 fl, where modal volumes were derived from volume frequency histograms. Non-glomerular and mixed are classified as negative)	Previously established diagnosis (established glomerular disease)	57	0	40	41	58.8	100.0	NC	0.41	NC
Game (2003)[93]	Urinary RBC volume ('glomerular' RBC volume distribution curve. Non-glomerular and mixed results are defined as negative. Cut-off values not reported)	Final diagnosis (glomerular diagnosis)	14	5	2	7	87.5	58.3	2.1	0.21	9.8
Game (2003)[93]	Urinary RBC volume ('non-glomerular' RBC volume distribution curve. Glomerular and mixed results are defined as negative. Cut-off values not reported)	Final diagnosis (non-glomerular diagnosis)	3	0	9	16	25.0	100.0	NC	0.75	NC

continued

TABLE 14 *Results of studies of automated analysis methods for the localisation of bleeding in patients with haematuria (cont'd)*

Study details	Index test (definition of a +ve test)	Reference test (definition of +ve test)	TP	FP	FN	TN	Sensitivity	Specificity	LR+	LR–	DOR
Hyodo (1997)[99]	Urinary RBC volume (non-glomerular: >80% of all RBCs were equal to or larger than the forward scatter intensity (FSC) of 84. Glomerular and mixed patterns are classified as negative)	Previously established diagnosis (diagnosis of non-glomerular disease)	42	0	5	19	89.4	100.0	NC	0.11	NC
Hyodo (1997)[99]	Urinary RBC volume (glomerular: >80% of all RBCs were equal to or smaller than the FSC of 126. Non-glomerular and mixed patterns are classified as negative)	Previously established diagnosis (diagnosis of glomerular disease)	19	2	0	45	100.0	95.7	23.5	0.00	NC
Hyodo (1999) [100]	Urinary RBC volume (non-glomerular: ≥80% of RBCs have an FSC intensity of at least 84 and less than 80% of all RBCs have FSC intensities of 126 or less. Glomerular and mixed classified as negative	Previously established diagnosis (non-glomerular disease)	71	0	11	26	86.6	100.0	NC	0.13	NC
Hyodo (1999)[100]	Urinary RBC volume (non-glomerular: ≥80% isomorphic cells. Glomerular and mixed are classified as negative)	Previously established diagnosis (non-glomerular disease)	62	0	5	31	92.5	100.0	NC	0.07	NC

continued

TABLE 14 *Results of studies of automated analysis methods for the localisation of bleeding in patients with haematuria (cont'd)*

Study details	Index test (definition of a +ve test)	Reference test (definition of +ve test)	TP	FP	FN	TN	Sensitivity	Specificity	LR+	LR–	DOR
Hyodo (1999)[100]	Urinary RBC volume (glomerular: ≥80% of RBCs have an FSC intensity of 126 or less and less than 80% of all RBCs have FSC intensities of at least 84. Non-glomerular and mixed are classified as negative)	Previously established diagnosis (glomerular disease)	26	6	0	76	100.0	92.7	13.7	0.00	NC
Hyodo (1999)[100]	Urinary RBC volume (glomerular: ≥80% dysmorphic RBCs. Non-glomerular and mixed are classified as negative)	Previously established diagnosis (glomerular disease)	28	0	3	67	90.3	100.0	NC	0.10	NC
Shichiri (1988)[114]	Urinary RBC size (glomerular: standard urinary RBC volume distribution with a peak at lower volume than that of peripheral RBC. Non-glomerular and mixed distributions are classified as negative)	Final diagnosis	65	16	2	63	97.0	79.7	4.8	0.04	128.0
Shichiri (1988)[114]	Urinary RBC size (non-glomerular: standard urinary RBC volume distribution with a peak at a higher volume than that of peripheral RBC. Glomerular and mixed distributions are classified as negative)	Final diagnosis	16	0	63	67	20.3	100.0	NC	0.80	NC

NC, not calculated, zero denominator.

TABLE 15 *Results of studies of other methods for the localisation of bleeding in patients with haematuria*

Study details	Index test (definition of a +ve test)	Reference test (definition of +ve test)	TP	FP	FN	TN	Sensitivity	Specificity	LR+	LR–	DOR
Single threshold											
Gimbel (1988)[95]	Urinary RBC size (glomerular: ≥5.7 μm)	Final diagnosis (diagnosed glomerular bleeding)	34	6	1	52	97.1	89.7	9.4	0.03	294.7
Tomita (1992)[116]	DIM (glomerular: ≥15% summed glomerular shapes)	Previously established diagnosis (established glomerular disease: diagnoses included IgA nephropathy, lupus nephritis, membrano-proliferative glomerulonephritis, non-IgA mesangial proliferative glomerular nephritis, Henoch–Schoenlein purpura nephritis, membranous nephropathy, endocapillary proliferative glomerularnephritis, and minimal change nephrotic syndrome)	66	1	7	39	90.4	97.5	36.2	0.10	367.7
Tomita (1992)[116]	DIM (glomerular: >1% doughnut-like cells with one or more blebs)	Previously established diagnosis (established glomerular disease: diagnoses included IgA nephropathy, lupus nephritis, membrano-proliferative glomerulonephritis, non-IgA mesangial proliferative glomerular nephritis, Henoch–Schoenlein purpura nephritis, membranous nephropathy, endocapillary proliferative glomerulonephritis, and minimal change nephrotic syndrome)	65	2	8	38	89.0	95.0	17.8	0.12	154.4
Kohler (1991)[104]	PCM, urinary RBC morphology (glomerular: ≥2% acanthocyturia)	Final diagnosis (biopsy–proven glomerulonephritis)	113	10	30	177	79.0	94.7	14.8	0.22	66.7

continued

TABLE 15 *Results of studies of other methods for the localisation of bleeding in patients with haematuria (cont'd)*

Study details	Index test (definition of a +ve test)	Reference test (definition of +ve test)	TP	FP	FN	TN	Sensitivity	Specificity	LR+	LR–	DOR
Kohler (1991)[104]	PCM, urinary RBC morphology (Glomerular: ≥5% acanthocyturia)	Final diagnosis (biopsy-proven glomerulonephritis)	75	4	68	183	52.4	97.9	24.5	0.49	50.5
Kohler (1991)[104]	PCM, urinary RBC morphology (Glomerular: ≥10% acanthocyturia)	Final diagnosis (biopsy-proven glomerulonephritis)	51	1	92	186	35.7	99.5	66.7	0.65	103.1
Dual threshold											
Chu (1990)[81]	DIM (non-glomerular: >80% of RBCs undistorted and uniform in size and shape. Glomerular and mixed classified as negative)	Previously established diagnosis (haematuria of non-glomerular origin)	17	3	0	15	100.0	83.3	6.0	0.00	NC
Chu (1990)[81]	DIM (non-glomerular: <10% of RBCs with glomerular morphology. Glomerular and mixed classified as negative)	Previously established diagnosis (haematuria of non-glomerular origin)	16	0	1	18	94.1	100.0	NC	0.06	NC
Chu (1990)[81]	DIM (glomerular: >20% of RBCs with glomerular morphology. Non-glomerular and mixed classified as negative)	Previously established diagnosis (haematuria of glomerular origin)	16	0	2	17	88.9	100.0	NC	0.11	NC
Chu (1990)[81]	DIM (glomerular: >80% of RBCs distorted with variation in size and shape, and fragmentation. Non-glomerular and mixed are classified as negative)	Previously established diagnosis (haematuria of glomerular origin)		13	0	5	17	72.2	100.0	NC	0.28
Hirakawa (1994)[97]	Confocal reflecting-laser microscopy (CRLM) (non-glomerular: >70% of normal red cells. Glomerular and mixed are classified as negative)	Final diagnosis (urological disease)	31	0	2	17	93.9	100.0	NC	0.06	NC

continued

TABLE 15 *Results of studies of other methods for the localisation of bleeding in patients with haematuria (cont'd)*

Study details	Index test (definition of a +ve test)	Reference test (definition of +ve test)	TP	FP	FN	TN	Sensitivity	Specificity	LR+	LR–	DOR
Hirakawa (1994)[97]	CRLM (glomerular: >70% dysmorphic red cells. Non-glomerular and mixed are classified as negative)	Final diagnosis (nephritis)	13	0	4	33	76.5	100.0	NC	0.24	NC
Hirakawa (1995)[98]	CRLM (non-glomerular: >70% of isomorphic (normal) red cells. Glomerular and mixed are classified as negative)	Final diagnosis (urological disease)	101	1	4	9	96.2	90.0	9.6	0.04	227.3
Hirakawa (1995)[98]	CRLM (glomerular: >70% of dysmorphic red cells. Non-glomerular and mixed are classified as normal)	Final diagnosis (glomerular disease)	8	0	2	105	80.0	100.0	NC	0.20	NC
Hyodo (1995)[101]	Laser microscopy, Hyodo-lino-Miyagawa (HIM) method (glomerular: ≥ 80% RBCs classified as showing a glomerular pattern. Non-glomerular and mixed are classified as negative)	Previously established diagnosis (clinical diagnosis of glomerular disease)	34	1	9	58	79.1	98.3	46.7	0.21	219.1
Hyodo (1995)[101]	Laser microscopy, HIM method (non-glomerular: ≥80% RBCs classified as showing a non-glomerular pattern. Glomerular and mixed are classified as negative)	Previously established diagnosis (clinical diagnosis of urological disease)	53	0	6	43	89.8	100.0	NC	0.10	NC

NC, not calculated, zero denominator.

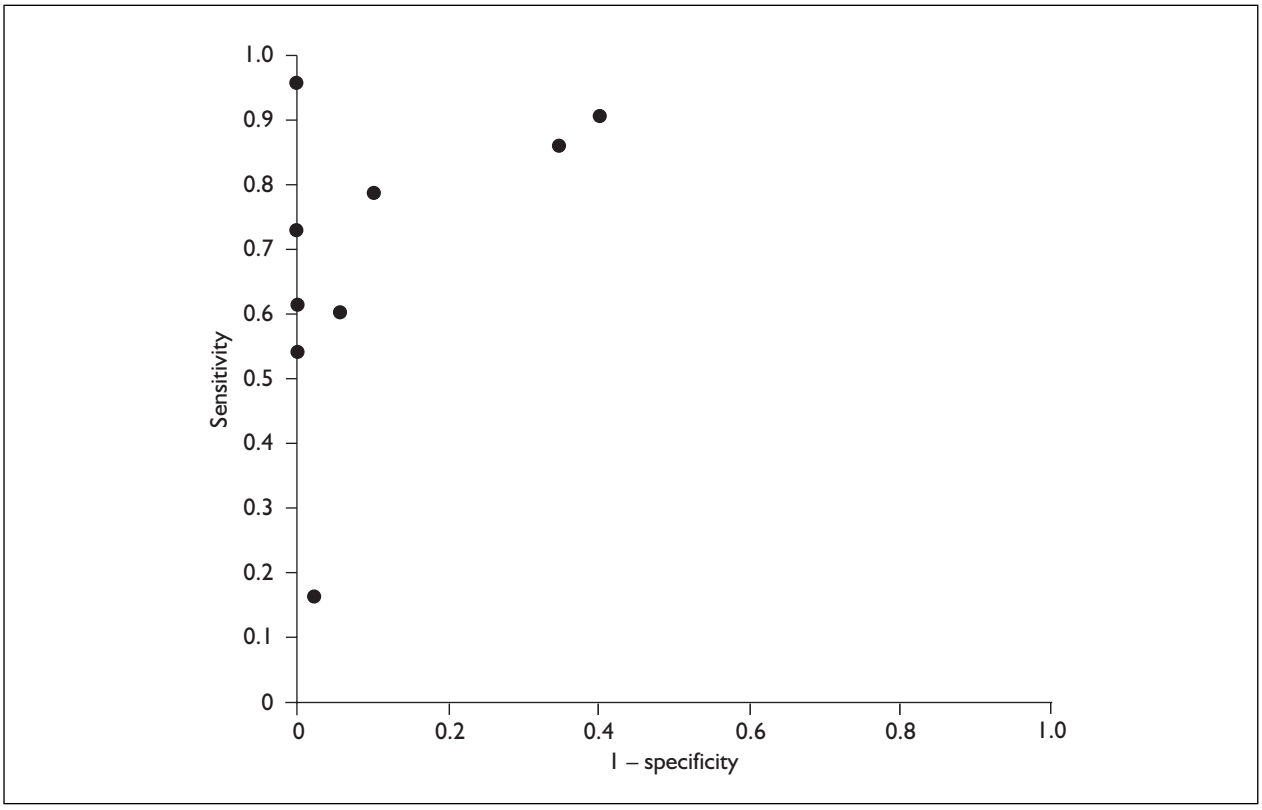


FIGURE 3 *Localisation of bleeding using light microscopy: study sensitivity and 1 – specificity plotted in ROC space*

Conventional light microscopy

Thirteen studies evaluated the diagnostic accuracy of light microscopy as a test to localise the source of bleeding in patients with haematuria (see *Table 12*).[75,81,82,84,91,92,102,105,107,110,112,115,117] The majority of these (ten) were diagnostic case–control studies (using a previously established diagnosis as the reference standard) and the remainder used final diagnosis as the reference standard.[82,92,115] The index test thresholds above which glomerular haematuria was diagnosed varied from 1 to 90% dysmorphic cells. Where multiple thresholds were examined in the same study,[82,102,112] estimates of diagnostic accuracy behaved as might be anticipated, with very high cut-off values resulting in high specificities and poor sensitivities and very low cut-off values resulting in high sensitivities and poor specificities. Although there was considerable variation in the specificities reported for low cut-off values, high cut-off values (70 or 80% dysmorphic RBCs) generally resulted in high specificities, suggesting that microscopic study of RBC morphology may have some utility for ruling in a renal cause for haematuria. It can equally be seen, however, that the cut-off value providing optimum diagnostic accuracy estimates differed considerably between each of these studies (e.g. Janssens and colleagues[102] >60%, Chu and colleagues[81] >20%).

For the 13 studies of light microscopy to detect a glomerular source of haematuria, sensitivity ranged from 16% (specificity 98%) to 96% (specificity 100%). Specificity ranged from 60% (sensitivity 90%) to 100% (sensitivity 54, 61, 73, 95, 96%). LR+ ranged from 2.26 (LR– = 0.16) to 64.25 (LR– = 0.06). LR– ranged from 0.86 (LR+ = 7.81) to 0.05 (LR+ = 7.64). The pooled LR+ was 9.24 (95% CI: 3.81 to 22.4) and the pooled LR– was 0.22 (95% CI: 0.11 to 0.46). The pooled LR+ value should be interpreted with extreme caution because the studies are clinically and statistically heterogeneous, as illustrated by *Table 12* and the estimates of sensitivity and 1 – specificity plotted in ROC space shown in *Figure 3*.

A regression analysis was carried out to investigate possible explanations for the observed heterogeneity. The regression model $D = \alpha + \beta S$ was extended to include variables for methodological quality in the form of QUADAS items. Univariate regression analysis showed that the relationship between description of the reference standard and DOR was significant at the

10% level. The DOR was around 26 times greater for studies that provided details of the reference standard than those that did not [RDOR 26.04 (95% CI: 1.20 to 565.26), $p = 0.04$].

Phase contrast microscopy

Twenty-two of the localisation studies specifically evaluated the diagnostic accuracy of phase-contrast microscopy (PCM) (*Table 13*).[73,74,78,80,81,83–85,89,90,92–94,96,105,106,108,109,111,115,118,119] Nine of these studies used a diagnostic case–control design[74,80,81,83,84,94,105,108,111] and 12 used the final diagnosis as the reference standard.[73,78,85,89,90,92,93,96,106,109,115,119] One study reported two data sets, one using the case–control design and one using final diagnosis as the reference standard.[118] The index test thresholds above which glomerular haematuria was diagnosed varied from 10 to 80% dysmorphic cells. Again, where multiple thresholds were examined in the same study, it could be seen that as cut-offs (in terms of percentage of dysmorphic RBCs) increased, so did specificity values, with a corresponding decrease in sensitivity values. Within these studies, there did not appear to be a single threshold that produced simultaneously high estimates of sensitivity and specificity. Looking across all PCM studies at wherever both sensitivity and specificity exceed 90%, the corresponding cut-offs (where stated) vary widely: 15%,[78] 20%,[115] 35%,[96] 40%,[111] 50%[96] and 80%.[85,119] However, in line with the results for light microscopy, a cut-off value of 80% dysmorphic RBCs consistently resulted in high specificities.

For the group of PCM studies, sensitivity ranged from 4% (specificity 86%) to 100% (specificity 94%). Specificity ranged from 59% (sensitivity 65%) to 100% (sensitivity 25, 61, 65, 69, 95%). LR+ ranged from 0.25 (LR– = 1.13) to 81.39 (LR– = 0.07). LR– ranged from 1.13 (LR+ = 0.25) to 0.01 (LR+ = 21.25). The pooled LR+ was 10.09 (95% CI: 5.47 to 18.64) and the pooled LR– was 0.19 (95% CI: 0.11 to 0.32). One study was excluded from pooling as it was a dual threshold study where patients with results between the thresholds had been excluded from the 2×2 data (i.e. it was not possible to dichotomise the results).[119] The pooled LR+ value should be interpreted with extreme caution because the studies are clinically and statistically heterogeneous, as illustrated by *Table 13* and the estimates of sensitivity and 1 – specificity plotted in ROC space shown in *Figure 4*.

A regression analysis was carried out to investigate possible explanations for the observed heterogeneity. The regression model $D = \alpha + \beta S$ was extended to include variables for methodological quality in the form of QUADAS items. Univariate regression analysis showed no significant variables at the 10% level.

Automated analysis

Fourteen studies evaluated automated methods that examined RDCs to localise the source of bleeding in patients with haematuria (*Table 14*).[21,75–77,79,86,87,93,99,100,103,108,113,114]

Seven of these studies used a diagnostic case–control design[79,99,100,103,108,113,535] and seven used the final diagnosis as the reference standard.[21,76,77,86,87,93,114] As with light microscopy and PCM, definitions of a positive index test varied widely. However, unlike those microscopy techniques where different cut-offs of a common measure (percentage of dysmorphic RBCs) were reported, automated analysis studies used a range of measures based on the principle of volumetric analysis of RBC volume, for example, RBC size, shape of cell volume distributions or the percentage of cells above/below set thresholds. This makes it difficult to observe any consistent pattern of results across studies.

For these automated analysis studies, sensitivity ranged from 59% (specificity 100%) to 100% (specificity 93, 96, 97, 100%). Specificity ranged from 58% (sensitivity 88%) to 100% (sensitivity 59, 100%). LR+ ranged from 2.1 (LR– = 0.21) to 97.08 (LR– = 0.01). LR– ranged from 0.42 (LR+ = 49.29) to 0.01 (LR+ = 97.08). The pooled LR+ was 7.86 (95% CI: 4.81 to 12.84) and the pooled LR– was 0.10 (95% CI: 0.05 to 0.23). The pooled LR+ value should be interpreted with extreme caution because the studies are clinically and statistically heterogeneous, as illustrated by *Table 14* and the estimates of sensitivity and 1 – specificity plotted in ROC space shown in *Figure 5*.

A regression analysis was carried out to investigate possible explanations for the observed heterogeneity. The regression model $D = \alpha + \beta S$ was extended to include variables for methodological quality in the form of QUADAS items. Univariate regression analysis showed no significant variables at the 10% level.

Other localisation studies

Seven diagnostic accuracy studies did not fall within the above groupings (*Table 15*).[81,95,97,98,101,104,116] One light microscopy study evaluated using a urinary RBC size of ≥5.7 µm as a test for glomerular bleeding, reporting a sensitivity of

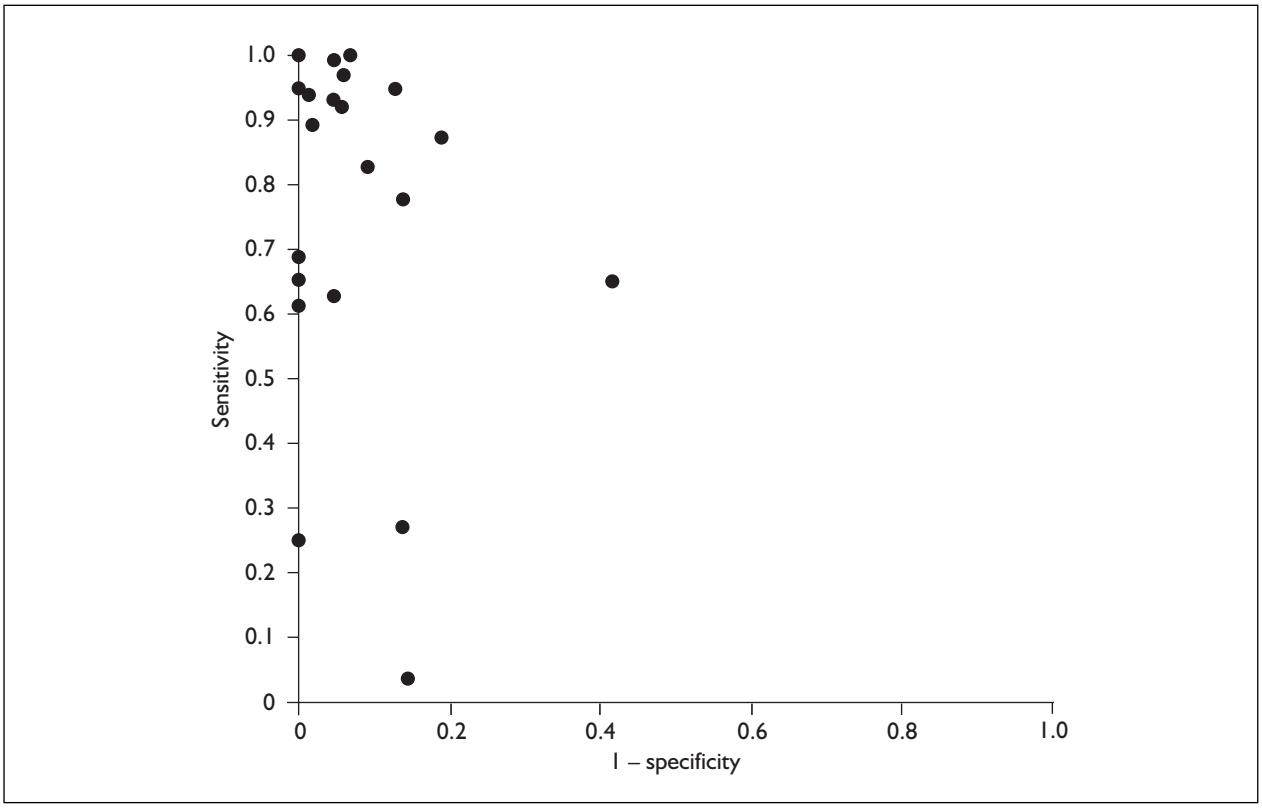


FIGURE 4 *Localisation of bleeding using PCM: study sensitivity and 1 – specificity plotted in ROC space*

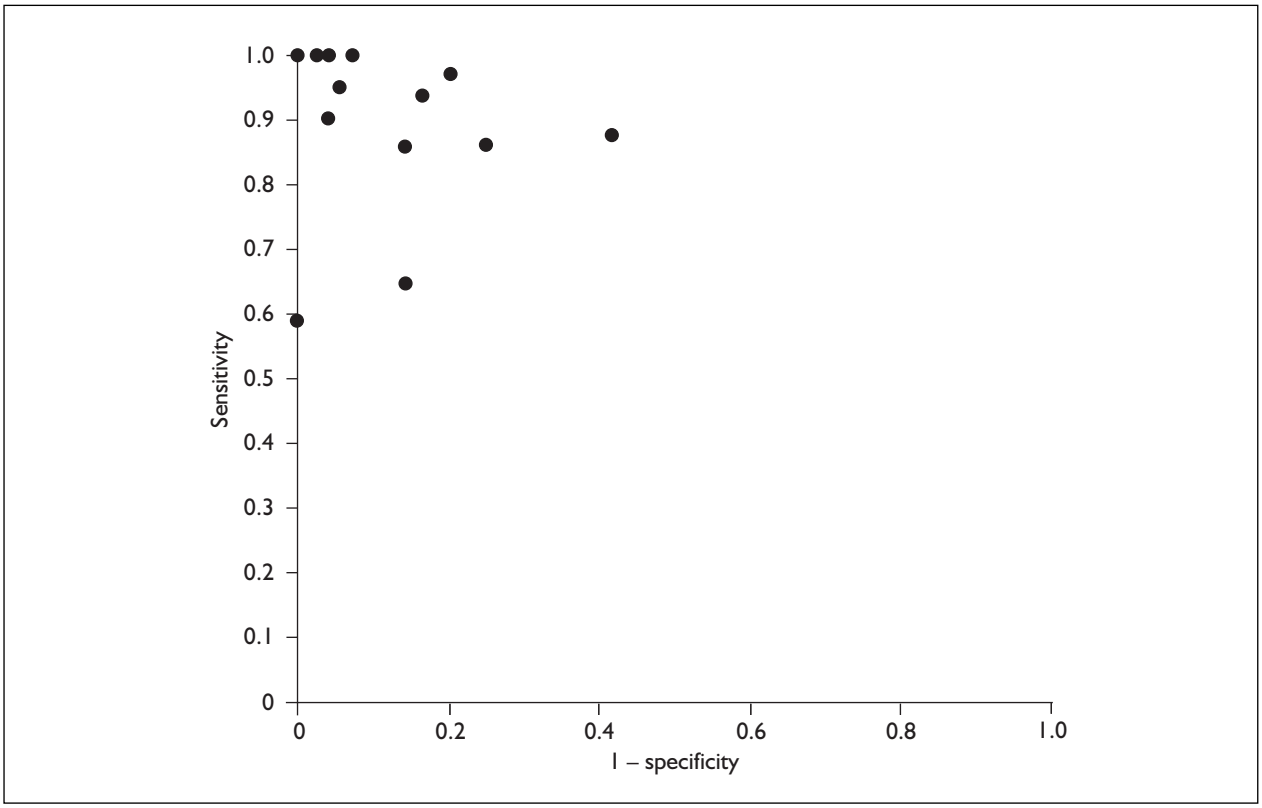


FIGURE 5 *Localisation of bleeding using automated analysis techniques: study sensitivity and 1 – specificity plotted in ROC space*

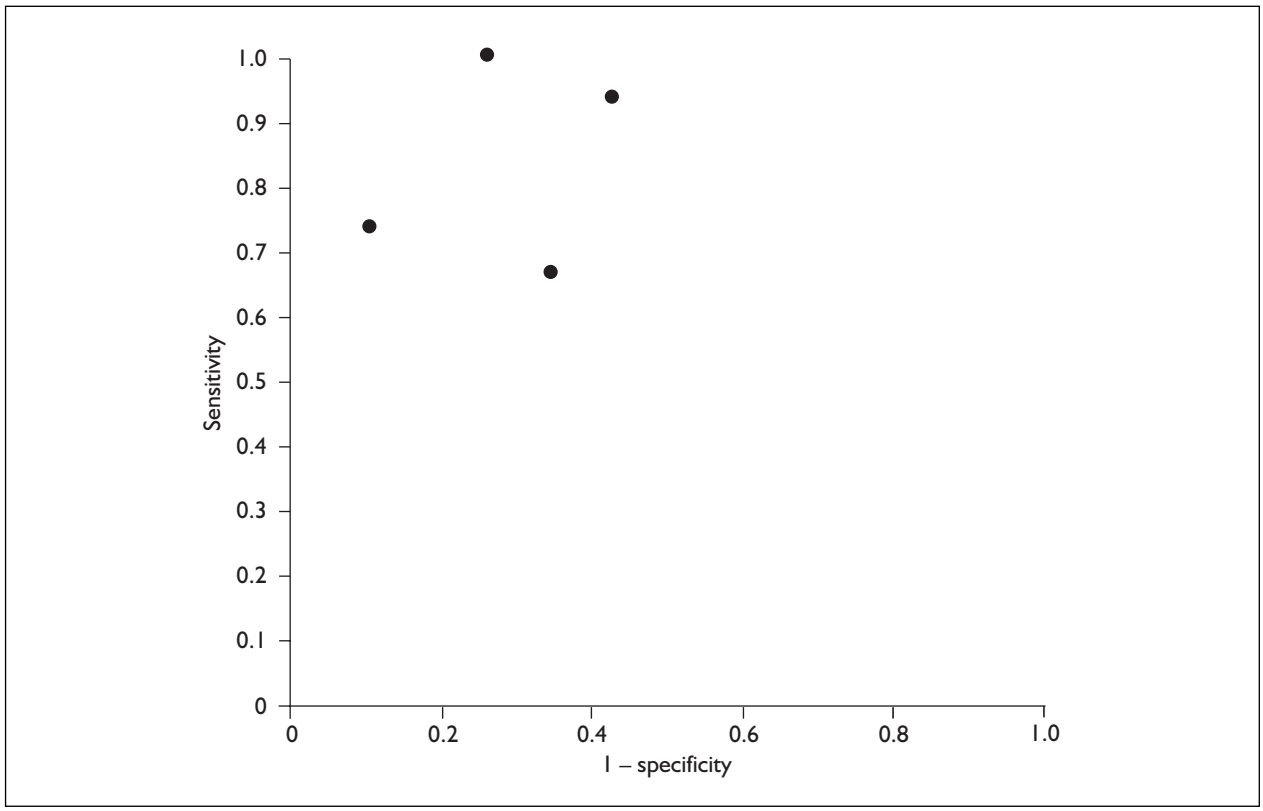


FIGURE 6 *BTA tumour marker: study sensitivity and 1 – specificity plotted in ROC space*

97.1% and specificity of 89.7%.[95] One PCM study specifically looked for the presence of acanthocytes (a specific type of dysmorphic RBC) rather than dysmorphic cells in general as an indicator of glomerulonephritis, reporting a cut-off of 2% acanthocyturia as the threshold yielding the overall best estimates of diagnostic accuracy (sensitivity 79%, specificity 95%).

Two studies specifically evaluated differential interference microscopy (DIM) as a method to identify dysmorphic RBCs in haematuria.[81,116] These studies presented different cut-offs for the DIM definition of a glomerular diagnosis (1%,[116] 15%,[116] 20%[81] and 80%[81]) with corresponding diagnostic accuracy values that were insufficient to pool or estimate an appropriate diagnostic threshold for this technique.

The three remaining studies evaluated laser microscopy techniques.[97,98,101] Two of these studies were by the same authors, used 70% of RBCs being dysmorphic as the cut-off for diagnosing glomerular disease and reported similar sensitivities (77% and 80%) and specificities (100% in both) for each study. The third laser microscopy study reported a different cut-off (80% dysmorphic RBCs), but similar estimates of diagnostic accuracy to the previous two (sensitivity 79%, specificity 98%).[101] Taken together, these results suggest that laser microscopy is a highly specific technique which might therefore be of use for ruling in a diagnosis of glomerular disease. However, further research is needed to confirm whether this is truly the case.

Detection of malignancies

Where urological malignancy is the target condition (usually bladder cancer), the reference standard of diagnosis is usually cystoscopy. Studies included in this review investigated a number of less invasive approaches to the diagnosis of malignancy. These were broadly categorised as biochemical tumour markers (measured in urine or plasma), cytological evaluation of urine samples or bladder washings and imaging techniques (used to investigate both benign and malignant lesions.

Tumour markers

Thirteen studies evaluated tumour markers for the detection of malignancy, primarily of the bladder.[29,123,125,127,129,135,138,140–143,148,1260] On the whole, these studies were poorly reported and/or were subject to numerous potential sources of bias. Studies met between five and nine of the 14 QUADAS validity criteria. Time between the index test and reference standard, whether blinding was

TABLE 16 *Results of studies of tumour markers for the detection of malignancy*

Study details	Index test (definition of a +ve test)	Reference test (definition of +ve test)	TP	FP	FN	TN	Sensitivity	Specificity	LR+	LR–	DOR
Chong (1999)[123]	BTA	Final diagnosis (malignant outcome)	8	12	4	23	66.7	65.7	1.9	0.51	3.8
Kirollos (1997)[129]	BTA	Cystoscopy (detection of urothelial malignancy)	1	6	0	17	100.0	73.9	3.8	0.00	NC
Quek (2002)[141]	BTA	IVU and cystoscopy with biopsy (bladder cancer confirmed by biopsy on cystoscopy)	15	31	1	42	93.8	57.5	2.2	0.11	20.3
Thomas (1996)[148]	BTA	Final diagnosis (histologically proven transition cell tumour)	17	28	6	244	73.9	89.7	7.2	0.29	24.7
Sarosdy (2004)[143]	FISH (bladder cancer)	Cystoscopy and/or biopsy (detection of bladder cancer)	34	81	16	325	68.0	80.0	3.4	0.40	8.5
Akaza (1997)[29]	NMP22 (12.0 U/ml)	Cystoscopy (diagnosis of urothelial cancer)	12	36	2	133	85.7	78.7	4.0	0.18	22.2
Miyanaga (1999)[134]	NMP22 (12 U/ml)	Final diagnosis	20	68	2	219	90.9	76.3	3.8	0.12	32.2
Miyoshi (2001)[135]	NMP22 (12.0 U/ml)	'Examination' [diagnosis of urothelial transitional cell carcinoma (TCC)]	14	32	10	171	58.3	84.2	3.7	0.49	7.5
Oge (2001)[138]	NMP22 (10 U/ml)	Cystoscopy	20	4	7	6	74.1	60.0	1.9	0.43	4.3
Paoluzzi (1999)[140]	NMP22 (≥10 U/ml)	Final diagnosis (diagnosis of TCC)	27	22	5	36	84.4	62.1	2.2	0.25	8.8
Glashan (1980)[125]	Plasma CEA (>40 ng/ml)	Final diagnosis	4	2	89	118	4.3	98.3	2.6	0.97	2.7
	Urine CEA (>35 ng/ml in males and >110 ng/ml in females)	Final diagnosis	21	30	36	90	36.8	75.0	1.5	0.84	1.8
Sanchez-Carbayo (2000)[142]	TPS (≥279 U/l)	Cystoscopy (diagnosis of bladder cancer)	26	7	13	43	66.7	86.0	4.8	0.39	12.3
	TPS/creatinine ratio (≥230 U/g creatinine)	Cystoscopy (diagnosis of bladder cancer)	26	13	13	37	66.7	74.0	2.6	0.45	5.7

continued

TABLE 16 *Results of studies of tumour markers for the detection of malignancy (cont'd)*

Study details	Index test (definition of a +ve test)	Reference test (definition of +ve test)	TP	FP	FN	TN	Sensitivity	Specificity	LR+	LR–	DOR
Jung (2002)[127]	UBCTM (>12 μg/l)	Final diagnosis (diagnosis of TCC)	17	12	2	53	89.5	81.5	4.8	0.13	37.5
NC, not calculated, zero denominator.											

undertaken or what clinical data were available when the tests were interpreted were rarely reported. Participant selection criteria were clearly described in only four studies[123,125,135,1260] and there were uninterpretable/intermediate results in five.[29,127,140,148,1260] However, the spectrum of included patients was generally representative of those who would receive the test in practice, and in most studies all of the patients received a reference standard that was independent of the index test and performed regardless of the index test result. The full results of QUADAS evaluation for studies assessing the diagnostic accuracy of tumour markers for the detection of malignancy are presented in *Table 16*.

In the majority of studies, the reference standard was cystoscopy[29,129,138,142] or final diagnosis.[123,125,127,135,140,148,1260] Two studies included cystoscopy with biopsy as the reference standard,[141,143] one of which also used IVU.[143] Four studies evaluated the BTA test; none of these reported the cut-off that would define a positive test result.[123,129,141,148] Five studies evaluated NMP22; one used a cut-off of 10 units/ml[140] and the others used 12 units/ml.[29,135,138,1260] Urinary and plasma carcinoembryonic antigen (CEA),[125] cytokeratin tissue polypeptide-specific antigen (TPS),[142] the fluorescent *in situ* hybridisation (FISH) assay[143] and urinary bladder cancer tumour marker (UBCTM) tests[127] were each evaluated in single studies.

For the four studies of BTA, sensitivity ranged from 67% (specificity 66%) to 100% (specificity 74%). Specificity ranged from 58% (sensitivity 94%) to 90% (sensitivity 74%). LR+ ranged from 1.94 (LR– = 0.51) to 7.18 (LR– = 0.29). LR– ranged from 0.51 (LR+ = 1.94) to 0.11 (LR+ = 2.21). The pooled LR+ was 3.09 (95% CI: 1.54 to 6.18) and the pooled LR– was 0.33 (95% CI: 0.2 to 0.55). The pooled LR+ value should be interpreted with caution owing to the presence of significant heterogeneity ($p < 0.001$). *Figure 6* shows estimates of sensitivity and 1 – specificity from the four BTA studies plotted in ROC space.

A regression analysis was carried out to investigate possible explanations for the observed heterogeneity. The regression model $D = \alpha + \beta S$ was extended to include variables for methodological quality in the form of QUADAS items. Univariate regression analysis showed no significant variables at the 10% level.

Five studies evaluated NMP22, with sensitivity ranging from 58% (specificity 84%) to 91% (specificity 76%). Specificity ranged from 60% (sensitivity 74%) to 84% (sensitivity 58%). LR+ ranged from 1.85 (LR– = 0.43) to 4.02 (LR– = 0.18). LR– ranged from 0.5 (LR+ = 3.7) to 0.12 (LR+ = 3.84). The pooled LR+ was 3.17 (95% CI: 2.35 to 4.28) and the pooled LR– was 0.31 (95% CI: 0.18 to 0.53). The pooled LR+ and LR– values should be interpreted with caution owing to the presence of significant heterogeneity ($p = 0.023$ and $p = 0.09$, respectively). *Figure 7* shows estimates of sensitivity and 1 – specificity from the five NMP22 studies plotted in ROC space.

A regression analysis was carried out to investigate possible explanations for the observed heterogeneity (*Table 17*). The regression model $D = \alpha + \beta S$ was extended to include variables for methodological quality in the form of QUADAS items. Univariate regression analysis showed that the adequate reporting of the details of the index test was the only significant QUADAS variable. The DOR was around four times higher in studies that did not adequately report index test details than in those that did [RDOR 4.35 (95% CI: 2.27 to 7.69), $p = 0.01$].

Compared with final diagnosis, one study reported urinary CEA[125] to have a sensitivity of 37% and a specificity of 75% (LR+ = 1.5, LR– = 0.84) and another reported a UBCTM test[127] to have a sensitivity of 90% and a specificity of 82% (LR+ = 4.8, LR– = 0.13). One study compared TPS with cystoscopy, reporting a sensitivity of 67% and a specificity of 86% (LR+ = 4.8, LR– = 0.39),[142] and the study of the FISH assay[143] reported a sensitivity of 68% and a specificity of 80% (LR+ = 3.4, LR– = 0.4).

Cytology

Fifteen studies evaluated cytology as a test for detecting urinary tract malignancy *Table 18*.[29,121,123,127,129,132,134–137,140,141,143,147,148] In general, these studies were poorly reported and/or were subject to numerous potential sources of bias. Studies met between five and nine of the 14 items on the QUADAS validity instrument. No study reported whether clinical data were available when the test results were being interpreted. Only once was the reference standard described[132] or the time between index and reference tests reported,[137] and very few studies clearly reported any attempts to limit review bias.[129,143,147] However, all but one study[29] clearly included an appropriate spectrum of patients, only two did not clearly confirm diagnosis with a reference standard in all participants[127,140] and all but three

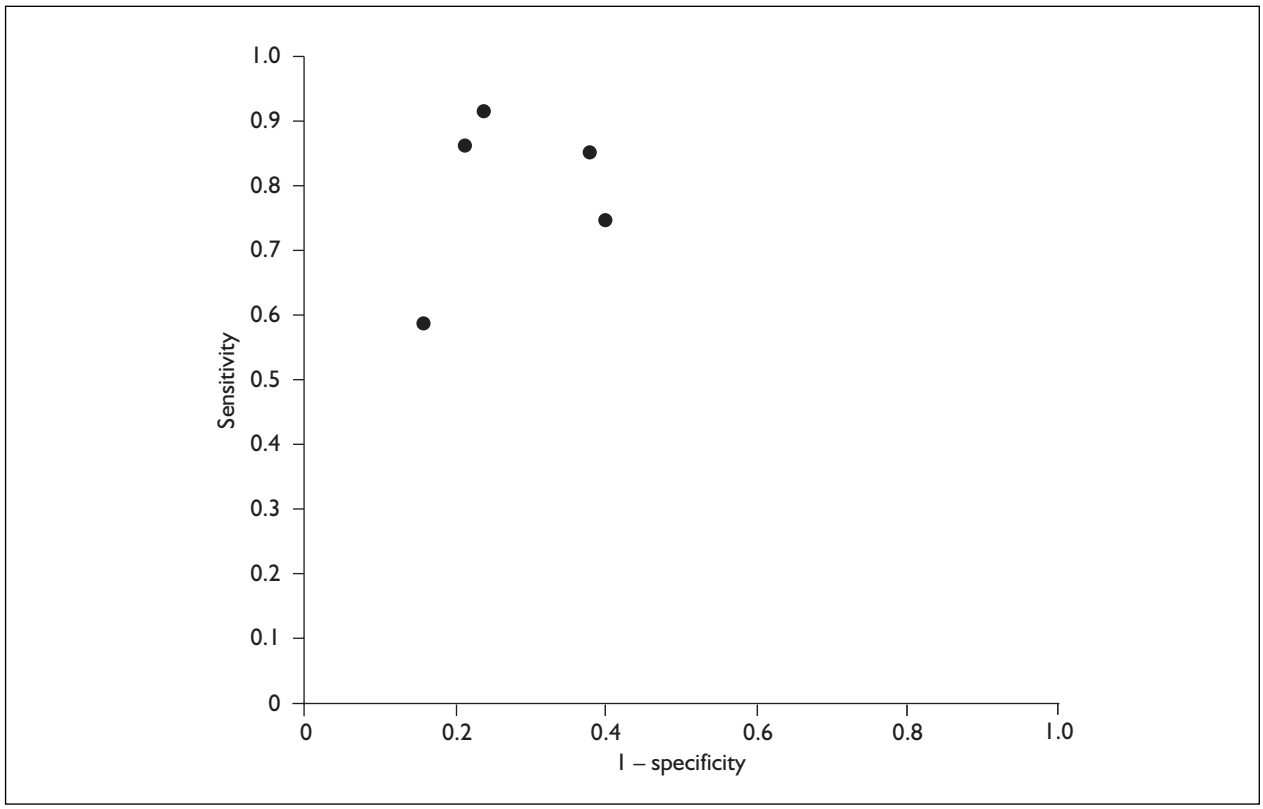


FIGURE 7 *NMP22 tumour marker: study sensitivity and 1 – specificity plotted in ROC space*

studies[121,127,135] reported using a reference standard that was likely to correctly classify the target condition. The full results of QUADAS evaluation for studies assessing the diagnostic accuracy of cytology for the detection of malignancy are presented in *Table 19*.

The majority of studies compared the findings of cystoscopy with 'final diagnosis'.[121,123,127,135,137,140,147,1260] In most studies where specific techniques were described, the reference standard consisted of cystoscopy,[29,129] histology[136,148] or both.[132,143] One study used a reference standard of IVU and cystoscopy.[141] Positive definitions for the index test were poorly described and included Papanicolau classification classes IV and V,[29,135,1260] bladder cancer,[136,143] transitional cell carcinoma,[127,140] and signs of malignancy.[121,132,147] One study reported the results of exfoliative cytology in voided urine versus lavage cytology for the same group of participants.[132] Data on exfoliative cytology were selected for comparison with the other study datasets.

Sensitivity ranged from 3% (specificity 99.5%) to 100% (specificity 100%). Specificity ranged from 62% (sensitivity 75%) to 100% (sensitivity 100, 67, 63, 47, 46%). LR+ ranged from 1.98 (LR– = 0.40) to 249 (LR– = 0.54). LR– ranged from 0.26 (LR+ = 36) to 0.97 (LR + = 6.53). The pooled LR+ was 17.9 (95% CI: 8.7 to 36.7) and the pooled LR– was 0.46 (95% CI: 0.27 to 0.81). These values should be interpreted with extreme caution owing to the presence of significant heterogeneity ($p <$ 0.001). The median LR+ was 27.5 (interquartile range: 8.45–76.3) and the median LR– was 0.53 (interquartile range: 0.39–0.55). *Figure 8* shows estimates of sensitivity and 1 – specificity plotted in ROC space.

A regression analysis was carried out to investigate possible explanations for the observed heterogeneity. The regression model $D = \alpha + \beta S$ was extended to include variables for methodological quality in the form of QUADAS items. Univariate regression analysis showed that the possible presence of disease progression bias and of differential verification bias was significant at the 10% level. The DOR was around 100 times lower in studies with an appropriate time between index test and reference standard than in those with the potential for disease progression bias [RDOR 0.01 (95% CI: 0.00 to 0.15), $p = 0.002$]. The DOR was around eight times higher in studies where all patients received the same reference standard regardless of index test result than in those with the potential for differential

TABLE 17 *QUADAS evaluation for studies of tumour markers for the detection of malignancy*

Study details	Appropriate spectrum composition	Selection criteria described	Appropriate reference standard	Disease progression bias avoided	Partial verification bias avoided	Differential verification bias avoided	Incorporation bias avoided	Test execution details reported adequately	Reference execution details reported adequately	Test review bias avoided	Diagnostic review bias avoided	Clinical review bias avoided	Uninterpretable results reported	Withdrawals accounted for
Chong (1999)[123]	Yes	Yes	Yes	Not clear	Yes	Not clear	Not clear	No	No	Not clear	Not clear	Not clear	Not clear	Yes
Kirollos (1997)[129]	Yes	No	Yes	Not clear	Yes	Yes	Yes	Yes	No	Yes	Yes	Not clear	Not clear	Yes
Quek (2002)[141]	Yes	No	Yes	Not clear	Yes	Yes	Yes	No	No	Not clear	Not clear	Not clear	Not clear	Yes
Thomas (1996)[148]	Yes	No	Yes	Not clear	Yes	Yes	Not clear	No	No	Not clear	Not clear	Not clear	Yes	No
Sarosdy (2004)[143]	Yes	No	Yes	Not clear	Yes	Yes	Yes	No	No	Yes	Yes	Not clear	Not clear	No
Akaza (1997)[29]	Not clear	No	Yes	Not clear	Yes	Yes	Yes	No	No	Not clear	Not clear	Not clear	Yes	Yes
Miyanaga (1999)[134]	Yes	Yes	Yes	Not clear	Yes	Yes	Yes	No	No	Not clear	Not clear	Not clear	Yes	Yes
Miyoshi (2001)[135]	Yes	Yes	Not clear	Not clear	Yes	Yes	Yes	No	No	Not clear	Not clear	Not clear	Not clear	Yes
Oge (2001)[138]	Not clear	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Not clear	Not clear	Not clear	Not clear	Yes
Paoluzzi (1999)[140]	Yes	No	Yes	Not clear	No	Yes	Yes	Yes	No	Not clear	Not clear	Not clear	Yes	Yes
Glashan (1980)[125]	Yes	Yes	Not clear	Not clear	Yes	Yes	Yes	No	No	Yes	Yes	No	Not clear	Yes
Sanchez-Carbayo (2000)[142]	Yes	No	Yes	Not clear	Yes	Yes	Yes	Yes	No	Not clear	Not clear	Not clear	Not clear	No
Jung (2002)[127]	Yes	No	Not clear	Not clear	Not clear	Not clear	Yes	Yes	No	Not clear	Not clear	Not clear	Yes	Yes

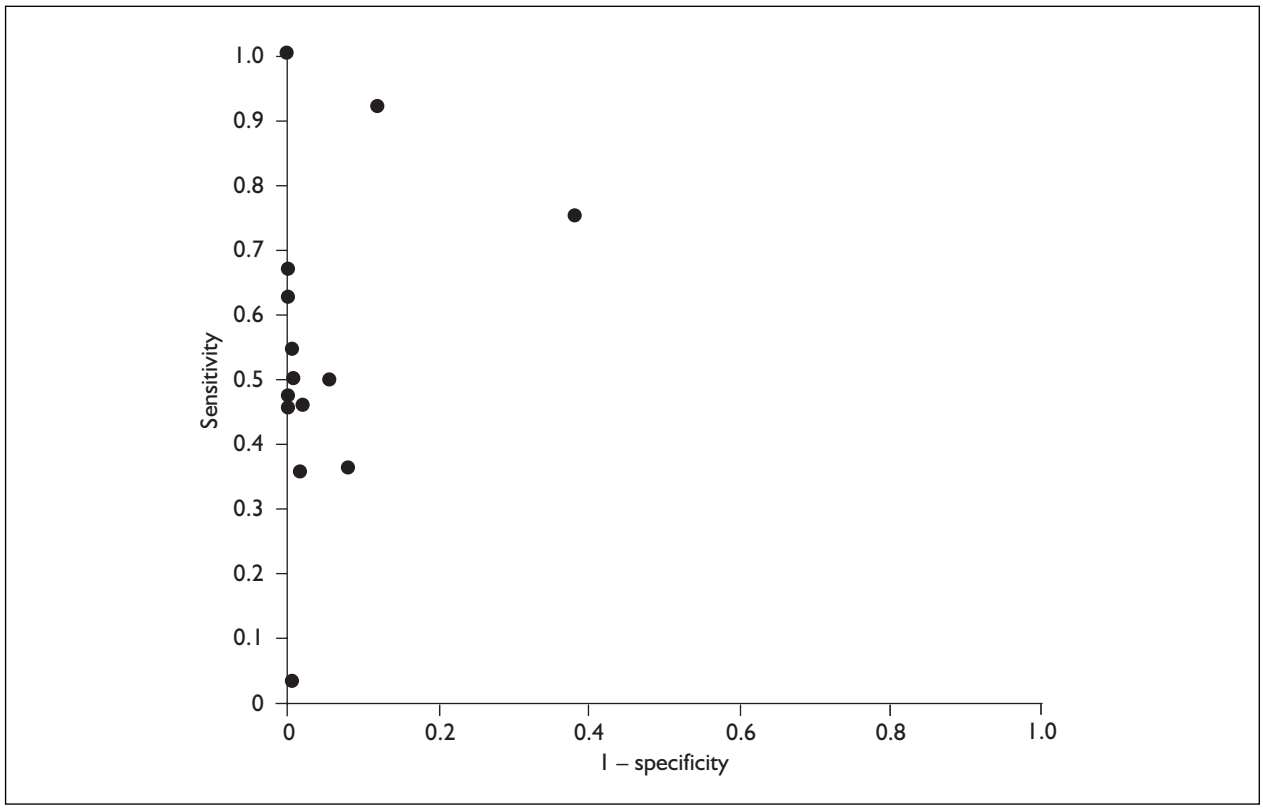


FIGURE 8 *Cytology: study sensitivity and 1 – specificity plotted in ROC space*

verification bias [RDOR 7.80 (95% CI: 1.04 to 58.57), $p = 0.05$]. Only disease progression bias remained significant at the 5% level in the multivariate model [RDOR 0.02 (95% CI: 0.00 to 0.50), $p = 0.02$].

Imaging techniques for investigation of the underlying cause of haematuria

Fifteen studies evaluated the diagnostic accuracy of imaging techniques to investigate the underlying cause of haematuria (*Table 20*).[120,122,124,126,128,130,131,133,137,139,144–146,149,150] There was a wide variation in methodological quality, with the studies meeting between two and 13 of the 14 QUADAS criteria. Most studies included an appropriate spectrum of patients, reported selection criteria, gave both the index and reference tests to all patients, and reported all uninterpretable results and withdrawals. Although all but two[128,133] of the 15 studies described the index test, only five described how the reference standard was executed. The full results of QUADAS evaluation for studies assessing the use of imaging techniques for the investigation of the underlying causes of haematuria are presented in *Table 21*.

The most frequently used reference standards were initial or final diagnosis. Other reference standards were IVU,[120,145,146] cystoscopy,[124,128] combined IVU and CT,[126] roentgenography,[133] and cytology[130] or histopathology[131] with urological follow-up.

The definition of a positive diagnosis also varied considerably between studies. Some studies assessed detection of any abnormality, whereas others focused on upper or lower tract, or malignancy or calculi.

Two studies investigated the use of CT to identify any abnormality that might cause haematuria.[126,131] One used CT combined with IVU as the reference standard,[126] reporting a sensitivity of 100% and a specificity of 97%. The other used histopathology and urological follow-up as a reference standard,[131] reporting a sensitivity and specificity for CT of 92% and 94%, respectively. The LR+ for these two studies were 30.8[126] and 16.5[131] [pooled LR+ 18.6 (95% CI: 10.8 to 32.1)] and the LR– were 0.01[126] and 0.08[131] [pooled LR– 0.05 (95% CI: 0.01 to 0.28)]. One of these CT studies reported considerably lower sensitivity for the detection of inflammatory and 'miscellaneous' lesions than for neoplasms.[131]

A third CT study evaluated the technique specifically as a method to identify filling defects or strictures in the urinary tract, reporting a

TABLE 18 *Results of studies of cytology for the detection of malignancy*

Study details	Index test (definition of a +ve test)	Reference test (definition of +ve test)	TP	FP	FN	TN	Sensitivity	Specificity	LR+	LR–	DOR
Single threshold											
Akaza (1997)[29]	Urine cytology [Papanicolau classification class IV and V (I, II and III as negative)]	Cystoscopy (diagnosis of urothelial cancer)	7	1	7	168	50.0	99.4	84.5	0.50	168.0
Chahal (2001)[121]	Features of malignancy were present, e.g. nuclear enlargement, increased nuclear/cytoplasmic ratio, hyperchromasia and irregular nuclear membrane thickness or contour. Features not clearly indicative of malignancy such as papillary clusters were reported as suspicious	Final diagnosis (any abnormality of the urinary tract)	24	13	24	224	50.0	94.5	9.1	0.53	17.2
Chong (1999)[123]		Final diagnosis (malignant outcome)	8	0	4	35	66.7	100.0	NC	0.33	NC
Jung (2002)[127]	Urine cytology (transitional cell carcinoma)	Final diagnosis (diagnosis of TCC)	9	0	10	65	47.4	100.0	NC	0.53	NC
Kirollos (1997)[129]	Urine cytology	Cystoscopy (detection of urothelial malignancy)	1	0	0	23	100.0	100.0	NC	0.00	NC
Misra (2000)[132]	Exfoliative urine cytology (loose clusters or isolated cells with increased nuclear cytoplasmic ratio with fine to coarse chromatin and prominent nucleoli)	Cystoscopy and biopsy (histologically confirmed tumour)	36	0	40	28	47.4	100.0	NC	0.53	NC
	Bladder washing (loose clusters or isolated cells with increased nuclear cytoplasmic ratio with fine to coarse chromatin and prominent nucleoli)	Cystoscopy and biopsy (histologically confirmed tumour)	54	0	22	28	71.1	100.0	NC	0.29	NC
Miyanaga (1999)[134]	Urine cytology (Papanicolou classes IV and V)	Final diagnosis	12	1	10	286	54.5	99.7	156.5	0.46	343.2

continued

TABLE 18 *Results of studies of cytology for the detection of malignancy (cont'd)*

Study details	Index test (definition of a +ve test)	Reference test (definition of +ve test)	TP	FP	FN	TN	Sensitivity	Specificity	LR+	LR–	DOR
Miyoshi (2001)[135]	Urine cytology [Papanicolau classification class IV and V (I, II and III as negative)]	'Examination' (diagnosis of urothelial TCC)	11	4	13	199	45.8	98.0	23.3	0.55	42.1
Mondal (1992)[136]	Urine cytology (bladder tumour. Transitional cell carcinomas were categorised as grade I, II, or III according to the degree of cellular pleomorphism and hyperchromatism and presence of inflammation and necrosis)	Histology (detection of bladder cancer)	92	11	8	82	92.0	88.2	7.8	0.09	85.7
Murakami (1990)[137]	Urine cytology [highly or moderately significant urological lesion, including malignancy (bladder, prostatic or renal pelvic cancer), or other significant lesion (e.g. urolithiasis, vesicoureteral reflux)]	Initial diagnosis (detection of any significant urological lesion)	7	4	208	798	3.3	99.5	6.5	0.97	6.7
Paoluzzi (1999)[140]	Urine cytology (transitional cell carcinoma)	Final diagnosis (diagnosis of TCC)	24	22	8	36	75.0	62.1	2.0	0.40	4.9
Quek (2002)[141]	Urine cytology	IVU and cystoscopy	10	0	6	73	62.5	100.0	NC	0.38	NC
Sarosdy (2004)[143]	Urine cytology (bladder cancer)	Cystoscopy and/or biopsy (detection of bladder cancer)	18	32	32	374	36.0	92.1	4.6	0.69	6.6
Sultana (1996)[147]	Urine cytology [upper tract calculi, isolated upper tract transitional cell carcinoma, hypernephroma or simple renal cyst (diameter > 2 cm)]	Final diagnosis (detection of urological malignancy)	21	6	38	454	35.6	98.7	27.3	0.65	41.8
Thomas (1996)[148]	Urine cytology	Final diagnosis (histologically proven transition cell tumour)	10	0	12	272	45.5	100.0	NC	0.55	NC

NC, not calculated, zero denominator.

TABLE 19 *QUADAS evaluation for studies of cytology for the detection of malignancy*

Study details	Appropriate spectrum composition	Selection criteria described	Appropriate reference standard	Disease progression bias avoided	Partial verification bias avoided	Differential verification bias avoided	Incorporation bias avoided	Test execution details reported adequately	Reference execution details reported adequately	Test review bias avoided	Diagnostic review bias avoided	Clinical review bias avoided	Uninterpretable results reported	Withdrawals accounted for
Akaza (1997)[29]	Not clear	No	Yes	Not clear	Yes	Yes	Yes	No	No	Not clear	Not clear	Not clear	Yes	Yes
Chahal (2001)[121]	Yes	Yes	Not clear	Not clear	Yes	No	Yes	No	No	Not clear	No	Not clear	Yes	Yes
Chong (1999)[123]	Yes	Yes	Yes	Not clear	Yes	Not clear	Not clear	No	No	Not clear	Not clear	Not clear	Not clear	Yes
Jung (2002)[127]	Yes	No	Not clear	Not clear	Not clear	Not clear	Yes	Yes	No	Not clear	Not clear	Not clear	Yes	Yes
Kirollos (1997)[129]	Yes	No	Yes	Not clear	Yes	Yes	Yes	Yes	No	Yes	Yes	Not clear	Not clear	Yes
Misra (2000)[132]	Yes	No	Yes	Not clear	Yes	Yes	Yes	Yes	Yes	Not clear	Not clear	Not clear	Not clear	Not clear
Miyanaga (1999)[134]	Yes	Yes	Yes	Not clear	Yes	Yes	Yes	No	No	Not clear	Not clear	Not clear	Yes	Yes
Miyoshi (2001)[135]	Yes	Yes	Not clear	Not clear	Yes	Yes	Yes	No	No	Not clear	Not clear	Not clear	Not clear	Yes
Mondal (1992)[136]	Yes	No	Yes	Not clear	Yes	Yes	Yes	Yes	No	Not clear	Not clear	Not clear	Yes	Yes
Murakami (1990)[137]	Yes	Yes	Yes	Yes	Yes	Not clear	Not clear	Yes	No	Not clear	Not clear	Not clear	Yes	Yes
Paoluzzi (1999)[140]	Yes	No	Yes	Not clear	No	Yes	Yes	Yes	No	Not clear	Not clear	Not clear	Yes	Yes
Quek (2002)[141]	Yes	No	Yes	Not clear	Yes	Yes	Yes	No	No	Not clear	Not clear	Not clear	Not clear	Yes
Sarosdy (2004)[143]	Yes	No	Yes	Not clear	Yes	Yes	Yes	No	No	Yes	Yes	Not clear	Not clear	No
Sultana (1996)[147]	Yes	Yes	Yes	Not clear	Yes	Yes	Not clear	No	No	Yes	Not clear	Not clear	Yes	No
Thomas (1996)[148]	Yes	No	Yes	Not clear	Yes	Yes	Not clear	No	No	Not clear	Not clear	Not clear	Yes	No

TABLE 20 *Results of studies of imaging techniques for investigation of the underlying cause of haematuria*

Study details	Index test (definition of a +ve test)	Reference standard (definition of +ve test)	TP	FP	FN	TN	Sensitivity	Specificity	LR+	LR–	DOR
Gray Sears (2002)[126]	CT (any abnormality)	IVP and CT (detection of any abnormality that can cause haematuria)	38	2	0	75	100.0	97.4	38.5	0.00	NC
Lang (2003)[130]	CT (any lesion of the lower urinary tract)	Cytology or urological follow-up (any lesion of the lower urinary tract)	26	4	12	205	68.4	98.1	35.8	0.32	111.0
	CT [lesion of the lower urinary tract (neoplasm)]	Cytology or urological follow-up [lesion of the lower urinary tract (neoplasm)]	10	0	0	237	100.0	100.0	NC	0.00	NC
	CT [lesion of the lower urinary tract (inflammatory)]	Cytology or urologic follow-up [lesion of the lower urinary tract (inflammatory)]	8	4	7	228	53.3	98.3	30.9	0.47	65.1
	CT [lesion of the lower urinary tract (miscellaneous)]	Cytology or urologic follow-up [lesion of the lower urinary tract (miscellaneous)]	8	0	5	234	61.5	100.0	NC	0.38	NC
Lang (2002)[131]	CT (any abnormality)	Histopathology/urological follow-up	158	10	13	169	92.4	94.4	16.5	0.08	205.4
O'Malley (2003)[139]	CT (filling defect or stricture in the urinary tract. A filling defect was defined as an abnormal structure that displaced contrast media in the urinary tract. A stricture was defined as a narrowing of the urinary tract with proximal dilation)	Final diagnosis (any abnormality of the urinary tract)	18	2	4	67	81.8	97.1	28.2	0.19	150.8
Cronan (1982)[124]	Cystosonography (bladder lesion)	Cystoscopy (detection of any bladder lesion)	12	3	2	83	85.7	96.5	24.6	0.15	166.0
Chisholm (1988)[122]	DMSA scintigraphy (any renal abnormality)	Final diagnosis (any renal abnormality)	10	4	0	49	100.0	92.5	13.3	0.00	NC
	IVU (any renal abnormality)	Final diagnosis (any renal abnormality)	9	1	1	52	90.0	98.1	47.7	0.10	468.0

continued

TABLE 20 *Results of studies of imaging techniques for investigation of the underlying cause of haematuria (cont'd)*

Study details	Index test (definition of a +ve test)	Reference standard (definition of +ve test)	TP	FP	FN	TN	Sensitivity	Specificity	LR+	LR–	DOR
Gray Sears (2002)[126]	IVU (any abnormality)	IVP and CT (detection of any abnormality that can cause haematuria)	23	7	15	70	60.5	90.9	6.7	0.43	15.3
Murakami (1990)[137]	IVU [highly or moderately significant urological lesion, including malignancy (bladder, prostatic or renal pelvic cancer), or other significant lesion (e.g. urolithiasis, vesicoureteral reflux)]	Initial diagnosis (detection of any significant urological lesion)	67	3	56	717	54.5	99.6	130.7	0.46	285.9
Speelman (1996)[144]	IVU (upper tract pathology)	Final diagnosis	6	25	3	263	66.7	91.3	7.7	0.37	21.0
Yip (1996)[149]	IVU [imaging detectable lesion (malignancy)]	Final diagnosis [detection of a lesion (malignancies)]	29	5	17	95	63.0	95.0	12.6	0.39	32.4
	IVU [imaging detectable lesion (calculi)]	Final diagnosis [detection of a lesion (calculi)]	8	0	6	132	57.1	100.0	NC	0.43	NC
Yip (1999)[150]	IVU (tumour of the lower tract)	Final diagnosis (diagnosis of a urological tumour of the lower tract)	45	7	35	365	56.3	98.1	29.9	0.45	67.0
	IVU (tumour of the upper tract)	Final diagnosis (diagnosis of a urological tumour of the upper tract)	32	21	4	395	88.9	95.0	17.6	0.12	150.5
O'Malley (2003)[139]	IVU (filling defect or stricture in the urinary tract. A filling defect was defined as an abnormal structure that displaced contrast media in the urinary tract. A stricture was defined as a narrowing of the urinary tract with proximal dilation)	Final diagnosis (any abnormality of the urinary tract)	15	3	7	66	68.2	95.7	15.7	0.33	47.1

continued

TABLE 20 *Results of studies of imaging techniques for investigation of the underlying cause of haematuria (cont'd)*

Study details	Index test (definition of a +ve test)	Reference standard (definition of +ve test)	TP	FP	FN	TN	Sensitivity	Specificity	LR+	LR–	DOR
Aslaksen (1990)[120]	Ultrasound (tumour of the urinary tract)	IVU (detection of a tumour of the urinary tract)	2	2	16	173	11.1	98.9	9.7	0.90	10.8
	Ultrasound (renal or ureteric calculi, defined as hyperechoic foci with a well-defined acoustic shadow. Suspected calculi with a diameter of ≥2 mm were not reported as positive findings)	IVU (detection of renal or ureteric calculi)	20	5	5	163	80.0	97.0	26.9	0.21	130.4
Murakami (1990)[137]	Ultrasound [highly or moderately significant urological lesion, including malignancy (bladder, prostatic or renal pelvic cancer), or other significant lesion (e.g. urolithiasis, vesicoureteral reflux)]	Initial diagnosis (detection of any significant urological lesion)	51	6	157	769	24.5	99.2	31.7	0.76	41.6
Speelman (1996)[144]	Ultrasound (upper tract pathology)	Final diagnosis	5	16	4	272	55.6	94.4	10.0	0.47	21.3
Spencer (1990)[145]	Ultrasound (any abnormality)	Intravenous urography (detection of any abnormality)	63	6	5	81	92.6	93.1	13.4	0.08	170.1
Steurer (1990)[146]	Ultrasound (any abnormality of the kidney or urinary tract)	IVP (any abnormality of the kidney or urinary tract)	5	1	1	14	83.3	93.3	12.5	0.18	70.0
Yip (1996)[149]	Ultrasound [imaging detectable lesion (malignancy)]	Final diagnosis [detection of a lesion (malignancies)]	44	8	2	92	95.7	92.0	12.0	0.05	253.0
	Ultrasound [imaging detectable lesion (calculi)]	Final diagnosis [detection of a lesion (calculi)]	11	0	3	132	78.6	100.0	NC	0.21	NC
Yip (1999)[150]	Ultrasound (tumour of the upper tract)	Final diagnosis (diagnosis of a urological tumour of the upper tract)	35	4	2	427	94.6	99.1	101.9	0.05	1868.1

continued

TABLE 20 *Results of studies of imaging techniques for investigation of the underlying cause of haematuria (cont'd)*

Study details	Index test (definition of a +ve test)	Reference standard (definition of +ve test)	TP	FP	FN	TN	Sensitivity	Specificity	LR+	LR–	DOR
	Ultrasound (tumour of the lower tract)	Final diagnosis (diagnosis of a urological tumour of the lower tract)	86	11	2	369	97.7	97.1	33.8	0.02	1442.5
Speelman (1996)[144]	Ultrasound and IVU (upper tract pathology)	Final diagnosis	7	35	2	253	77.8	87.8	6.4	0.25	25.3
Kim (2002)[128]	Virtual cystoscopy (any bladder lesion)	Cystoscopy (detection of any bladder lesion)	41	2	2	28	95.3	93.3	14.3	0.05	287.0
Mitty (1974)[133]	Angiography (cause of bleeding established)	Clinical and roentgenographic evaluation (cause of bleeding established)	6	0	14	28	30.0	100.0	NC	0.70	NC

NC, not calculated, zero denominator.

TABLE 21 *QUADAS evaluation for studies of imaging techniques for investigation of the underlying cause of haematuria*

Study details	Appropriate spectrum composition	Selection criteria described	Appropriate reference standard	Disease progression bias avoided	Partial verification bias avoided	Differential verification bias avoided	Incorporation bias avoided	Test execution details reported adequately	Reference execution details reported adequately	Test review bias avoided	Diagnostic review bias avoided	Clinical review bias avoided	Uninterpretable results reported	Withdrawals accounted for
Aslaksen (1990)[120]	Yes	No	Not clear	Not clear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Chisholm (1988)[122]	Yes	Yes	Yes	Not clear	Yes	Not clear	No	Yes	No	Not clear	Not clear	Not clear	Yes	Yes
Cronan (1982)[124]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Not clear	Yes	Yes
Gray Sears (2002)[126]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Not clear	Yes	Yes
Kim (2002)[128]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Not clear	Yes	Yes
Lang (2003)[130]	No	No	Not clear	Not clear	Not clear	Not clear	Yes	Yes	No	Not clear	Not clear	Not clear	Not clear	Not clear
Lang (2002)[131]	No	Yes	Not clear	Not clear	Yes	Not clear	Yes	Yes	No	Not clear	Not clear	Not clear	Not clear	Yes
Mitty (1974)[133]	Yes	Yes	Not clear	Not clear	Yes	Not clear	Yes	No	No	Not clear	Not clear	Not clear	Not clear	Yes
Murakami (1990)[137]	Yes	Yes	Yes	Yes	Yes	Not clear	Not clear	Yes	No	Not clear	Not clear	Not clear	Yes	Yes
O'Malley (2003)[139]	Yes	Yes	Yes	Not clear	Yes	Not clear	No	Yes	No	Yes	No	Yes	Yes	Yes
Speelman (1996)[144]	Yes	Yes	Not clear	Not clear	Yes	Yes	Not clear	Yes	No	Yes	Yes	Not clear	Yes	Yes
Spencer (1990)[145]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Yes	Yes
Steurer (1990)[146]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Yes	Yes
Yip (1996)[149]	Yes	Yes	Not clear	Not clear	Yes	Not clear	Not clear	Yes	No	Not clear	Not clear	Not clear	Yes	Not clear
Yip (1999)[150]	Yes	Yes	Yes	Not clear	Yes	Yes	Not clear	Yes	No	Yes	Not clear	Not clear	Yes	Yes

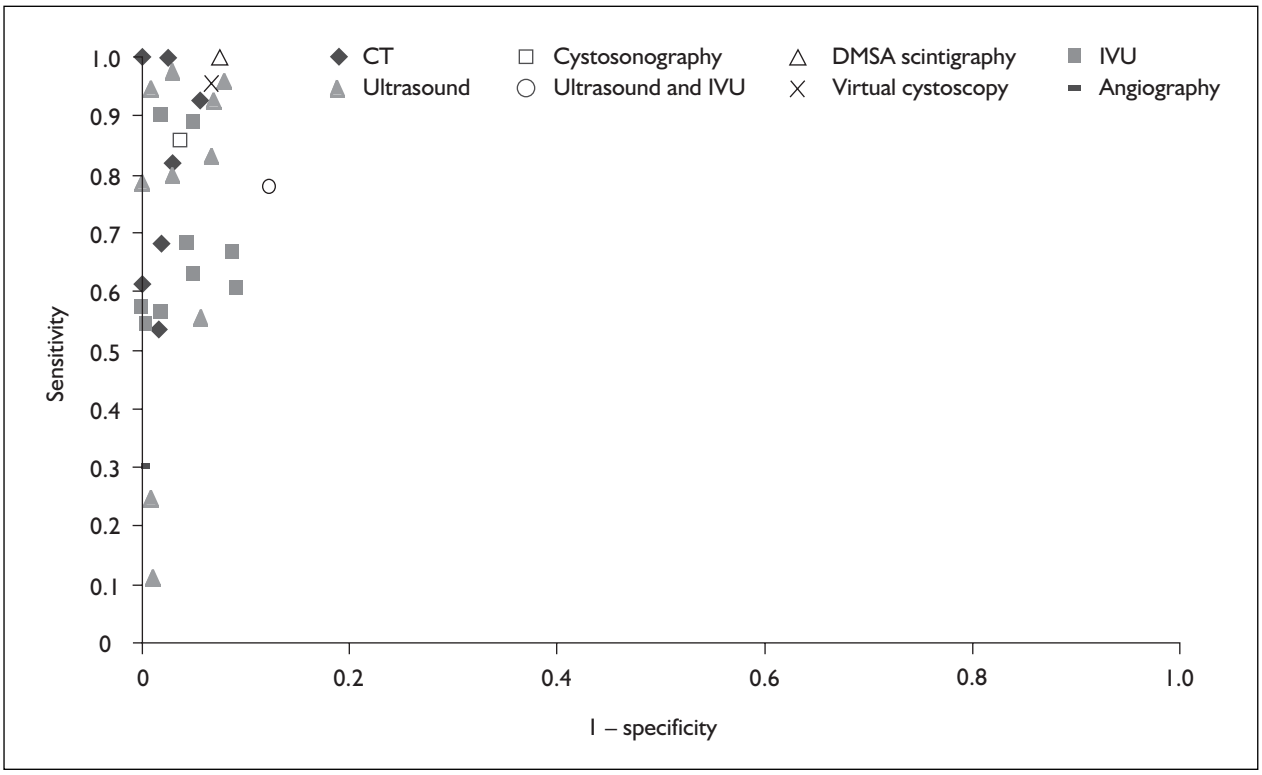


FIGURE 9 *Imaging: sensitivity and 1 – specificity plotted in ROC space for all study comparisons and diagnostic aims*

sensitivity of 82% and specificity of 97%.[139] These results suggest that there is some evidence to support the use of CT to determine the cause of haematuria. However, it should be borne in mind that these values are derived from just three accuracy studies, of which one was very poorly reported.[131] The included studies were also very general in their aims, assessing detection of any abnormality, and the limited evidence suggests that the diagnostic performance of CT may vary significantly with target condition.

Seven studies evaluated IVU as an index test.[122,126,137,139,144,149,150] Two evaluated IVU for the detection of any significant abnormality that could cause haematuria,[126,137] with reference standards being either combined IVU and CT[126] or 'initial diagnosis'.[137] These studies reported sensitivities of 61%[126] and 55%[137] and specificities of 91%[126] and 99%.[137] The LR+ were 6.7[126] and 130.7[137] and the LR– were 0.44[126] and 0.46.[137] A third (poorly reported) study compared IVU with final diagnosis for the detection of malignancies (sensitivity 63%, specificity 95%) and calculi (sensitivity 57%, specificity 100%).[149] The remaining IVU studies all evaluated IVU against final diagnosis, but for different target conditions: upper urinary tract tumours (sensitivity 89%, specificity 95%),[150] lower tract tumours (sensitivity 56%, specificity 98%),[150] any upper tract pathology (sensitivity 67%, specificity 91%),[144] any renal abnormality (sensitivity 90%, specificity 98%)[122] or any filling defect or structure in the urinary tract (sensitivity 68%, specificity 98%).[139] Across the IVU studies, specificity values (range 91–100%) appeared to be more consistent than sensitivity values (range 55–90%), although it is difficult to estimate the overall value of IVU as a test owing to the clinical and statistical heterogeneity between studies.

Six studies evaluated US as a test to detect the cause of haematuria.[137,144–146,149,150] Three of these focused on using US to identify any lesion or abnormality in the urinary tract.[137,145,146] These reported sensitivities of 25%,[137] 93%[145] and 83%,[146] and specificities of 99%,[137] 93%[145] and 93%.[146] The study which reported a sensitivity of 25% differed from the other two in that it used initial diagnosis (as opposed to IVU) as a reference standard and it focused on the detection of 'highly or moderately significant' lesions. Two studies separately reported the accuracy of US in detecting calculi and tumours/malignancy.[120,149] For calculi, the reported sensitivities were 80%[120] and 78%[149] and the reported specificities were 97%[120] and 100%.[149] For tumours/malignancy, the reported sensitivities were 11%[120] and 96%,[149] and

the reported specificities were 99%[120] and 92%.[149] It can be seen that estimates of specificity were generally high (although statistically heterogeneous) for both calculi and tumours, and whereas the estimates of sensitivity were statistically homogeneous for detecting calculi (78% versus 80%), they were markedly different for tumours (11% versus 99%). The studies also differed from one another in terms of clinical and methodological characteristics, making it difficult to draw any firm conclusions about the relative accuracy of US for detecting calculi versus tumours. One further US study reported separate results for the accuracy of US in detecting tumours (compared with final diagnosis) of the upper (sensitivity 95%, specificity 99%) and lower urinary tract (sensitivity 98%, specificity 97%).[150] Three studies compared US against IVU, using final diagnosis as a reference standard.[144,149,150] Specificity estimates appeared to be similar for both techniques (range 91–100%), whether investigating calculi or tumours, but were inconsistent across studies. As a whole, the group of six studies evaluating US were clinically, methodologically and statistically heterogeneous, and efforts to separate studies into sensible subgroups failed to yield any clear pattern of results.

Five more studies evaluated imaging modalities that differed from those described above.[122,124,128,133,144] These evaluated renal angiography for locating the source of renal bleeding (sensitivity 30%, specificity 100%),[133] US and IVU in combination for identifying upper tract pathologies (sensitivity 78%, specificity 88%),[144] dimercaptosuccinic acid (DMSA) scintigraphy for the identification of any renal abnormality (sensitivity 100%, specificity 93%),[122] virtual cystoscopy for the identification of bladder lesions (sensitivity 95%, specificity 93%),[128] and cystosonography for the identification of bladder lesions (sensitivity 86%, specificity 97%).[124] The reference tests in these studies were cystoscopy,[124,128] clinical/roentgenographic evaluation[133] and final diagnosis.[122,144]

Figure 9 shows the range in estimates of sensitivity and 1 – specificity for all 31 comparisons from the 15 imaging studies.

Chapter 7
Economic analyses

Economic evaluations included in the review

Six published studies met the inclusion criteria of full economic evaluations addressing a question related to the diagnosis of haematuria, either alone or in conjunction with its underlying causes.[28,70,269,1049,1088,1261]

In addition, two abstracts of full economic evaluations were identified.[863,953] Where a trace was possible regarding the affiliations of the authors, emails were sent requesting details of publications or models, but no responses were received. However, the abstracts addressed highly relevant questions and therefore a summary of the findings is presented in the following sections.

Data extraction of included studies

Data extraction was performed on the included six studies according to the methods adopted by NHS EED.[37] In addition, all resource use and unit cost data were extracted from each study. This additional information was considered to be useful in informing resource use and cost data for the decision analytic modelling.

The structured abstracts for each of the six studies are shown in Appendix 8.

Quality assessment of included studies

Critical textual summaries, as outlined in the section 'Economic evaluations' (p. 8), are shown for each of the six studies at the end of each structured abstract in Appendix 8.

The checklist, summary score and hierarchical matrix results for each study are shown in *Table 22* and further summarised in the next section.

Summary of included studies

None of the six studies included were conducted in the UK; five were conducted in the USA and one in Japan. Hence the cost data are likely to have limited generalisability to the UK context; the perspective adopted was mostly that of the third-party payer, and in some cases charges were used rather than costs. All six studies derived their effectiveness data from a single clinical study. No published modelling studies were found that dealt with testing for the presence of haematuria. However, the effectiveness, epidemiological and health outcome data were informative as a reference point with regard to decision analytic modelling

Hofland and Mariani[1261] examined the use of urine cytology to detect urothelial malignancy in the evaluation of patients with asymptomatic microscopic haematuria. The aim was to validate the AUA Best Practice Policy on Asymptomatic Microscopic Haematuria, which recommends cytology only in patients with risk factors (detailed in Appendix 8) for transitional cell carcinoma (TCC). The study evaluated how often urine cytology yielded supportive or unique information that led to the diagnosis of TCC, the cost of that information and whether it would have been obtained using the current best practice guidelines.

The study was conducted in Honolulu, Hawaii, USA, and used Medicare cost data. Effectiveness data were derived from a cohort study and the study sample comprised 1000 sequential patients who underwent a standardised haematuria evaluation.

The average cost to diagnose a life-threatening condition was $1521 for urine cytology, $1695 for IVP, $3044 for cystoscopy and $3291 for serum creatinine. The average cost to provide unique information was $8367 for urine cytology, $5616 for IVP, $3235 for cystoscopy and $3291 for serum creatinine.

The authors concluded that urine cytology is a useful test for adjusting a clinician's index of suspicion for patients undergoing a haematuria evaluation. The findings of this study supported the use of urine cytology only on high-risk patients, in accordance with the AUA guidelines.

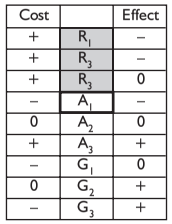
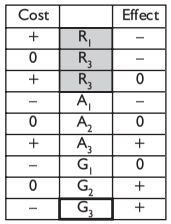
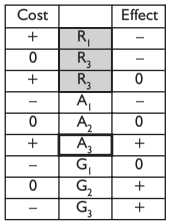
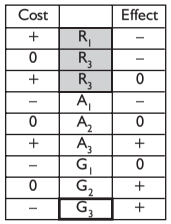
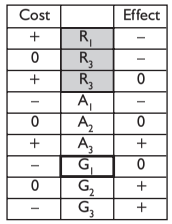
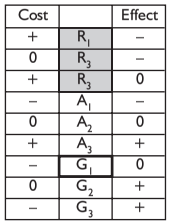
In terms of the quality checklist, the study adequately addressed 76% of applicable points, and the hierarchical matrix result was cell A_1, indicating that cytology generally cost less but was less effective than the comparator tests (except serum creatinine).

TABLE 22 *36-point checklist for included economic evaluations*

Question	Hofland (2004)[1261]	Mariani (1984)[1049]	Novicki (1998)[269]	Parekattil (2003)[70]	Wakui (2000)[1088]	Zippe (1999)[28]
Study design						
1. The research question is stated	Y	Y	Y	Y	Y	Y
2. The economic importance of the research question is stated	Y	Y	Y	Y	Y	Y
3. The viewpoint(s) of the analysis are stated	Y	N	Y	Y	Y	N
4. The rationale for choosing the alternative programmes or interventions are stated	Y	Y	Y	Y	Y	Y
5. The alternatives being compared are clearly described	Y	P	Y	Y	Y	Y
6. The form of economic evaluation is stated	Y	P	Y	P	Y	Y
7. The choice of form of economic evaluation is justified in relation to the questions addressed	P	N	N	N	Y	N
Data collection						
8. The source(s) of effectiveness estimates are stated	Y	Y	Y	Y	Y	Y
9. Details of the design and results of effectiveness study are given (if based on a single study)	Y	Y	Y	Y	Y	Y
10. Details of methods of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	NA	NA	NA	NA	NA	NA
11. The primary outcome measure(s) for the economic evaluation are clearly stated	Y	Y	Y	Y	Y	Y
12. Methods to value health states and other benefits are stated	NA	NA	NA	NA	NA	NA
13. Details from the subjects from whom valuations are obtained are given	NA	NA	NA	NA	NA	NA
14. Productivity changes (if included) are reported separately	NA	NA	NA	NA	NA	NA
15. The relevance of productivity changes to the study question is discussed	N	N	N	N	N	N
16. Quantities of resources are reported separately from their unit costs	Y	Y	N	Y	P	N
17. Methods for the estimation of quantities and unit costs are described	Y	P	Y	Y	Y	Y
18. Currency and price data are recorded	Y	Y	Y	Y	Y	Y
19. Details of currency of price adjustments for inflation or currency conversion are given	NA	NA	NA	NA	NA	NA
20. Details of any model used are given	NA	NA	NA	NA	NA	NA
21. The choice of model used and key parameters on which it is based are justified	NA	NA	NA	NA	NA	NA

continued

TABLE 22 *36-point checklist for included economic evaluations (cont'd)*

Question	Hofland (2004)[1261]	Mariani (1984)[1049]	Novicki (1998)[269]	Parekattil (2003)[70]	Wakui (2000)[1088]	Zippe (1999)[28]
Analysis and interpretation of results						
22. The horizon of costs and benefits is stated	Y	Y	Y	Y	Y	Y
23. The discount rate is stated	NA	N	NA	NA	NA	NA
24. The choice of rate is justified	NA	N	NA	NA	NA	NA
25. An explanation is given if costs or benefits are not discounted	NA	N	NA	NA	NA	NA
26. Details of statistical test and confidence intervals are given for stochastic data	N	N	N	N	N	N
27. The approach to sensitivity analysis is given	N	N	N	N	N	N
28. The choice of variables for sensitivity analysis is justified	NA	NA	NA	NA	NA	NA
29. The ranges over which the variables are varied is stated	NA	NA	NA	NA	NA	NA
30. Relevant alternatives are compared	NA	NA	NA	NA	NA	NA
31. Incremental analysis is reported	P	Y	Y	P	Y	Y
32. Major outcomes are reported in a disaggregated as well as aggregated form	Y	Y	Y	P	P	P
33. The answer to the study question is given	Y	Y	Y	Y	Y	Y
34. Conclusions followed from the data reported	Y	Y	Y	Y	Y	Y
35. Conclusions are accompanied by the appropriate caveats	Y	Y	Y	Y	Y	Y
36. Generalisability issues are addressed	N	N	N	N	P	N
Total Y	17.5	15	15	16.5	18.5	15
Total NA	13	10	13	13	13	13
Percentage of applicable items: (Y/36–NA) × 100	**76**	**58**	**65**	**72**	**80**	**65**
Hierarchical decision matrix showing direction of result (costs and effects)						

Y, Yes (score = 1); N, no (score = 0); NA not applicable; P, partial (score = 0.5).

Mariani and colleagues[1049] aimed to investigate the incidence and distribution of adult haematuria, and also the medical risk benefit and the cost-effectiveness of haematuria evaluation among different subgroups. The cost-effectiveness analysis examined the difference in costs between treating patients early (as a result of the evaluation for haematuria – see the abstract in Appendix 8 for details of technologies used) and treating them late through detection in normal clinical practice following the onset of symptoms. The authors also investigated the degree of haematuria versus the diagnostic yield of the chosen suite of tests. The comparator was 'do nothing.'

The study population comprised adult male and female patients with asymptomatic gross or microscopic haematuria, without significant proteinuria, and was derived from a multiracial, stable, closed Health Maintenance Organisation in the USA.

Effectiveness data were derived from a retrospective cohort study of 1000 consecutive patients. The epidemiological and health outcome findings were stratified according to different age groups (general population, 18–29, 30–39, 40–49, 50–59, 60–69, 70–79 years) and included the incidence of haematuria; incidence of life-threatening lesions; haematuria and diagnosis of genitourinary cancer; haematuria evaluation results; incidental findings; life-threatening risk of haematuria evaluation; and degree of haematuria versus diagnostic yield.

The economic analysis centred on the diagnosis (and survival) of a life-threatening lesion for early versus late detection and treatment. However, cost-effectiveness was based on only three patients in the sample who ignored symptoms of gross haematuria before presenting with pain, cachexia or life-threatening haemorrhage from metastasis bladder cancer. Their average survival was 17 months. These cases were compared with three patients who were diagnosed early (two with gross and one with microscopic haematuria), with two cases of localised bladder cancer and one of localised renal adenocarcinoma). These patients survived for at least an average of 17 months.

The results showed that the average cost to treat a patient with bladder cancer (metastatic) diagnosed and treated late was $58,475 (until death). The average cost to diagnose and treat similar patients diagnosed early was $9405 (based on a 17-month period). This was an incremental cost of $48,070. The authors noted that 92% of patients diagnosed with localised genitourinary malignancy were detected while the disease was still localised. The result suggests the intervention is highly cost-effective, as the additional cost is five times the cost of the evaluation for the 1000 patients studied.

The authors concluded that, for all categories studied, except for women under 40 years old with microscopic haematuria, the risk of haematuria evaluation was less than the incidence of life-threatening lesions discovered as a result of evaluation. Asymptomatic haematuria, whether gross or microscopic, was considered to be a significant finding and warrants evaluation from a risk–benefit and cost-effectiveness standpoint.

A major limitation of the study is that the effectiveness data for the economic evaluation were based on only three matched pairs of patients for early and late detection of malignancy and may not be reliable. However, the rationale for the approach to determine the cost-effectiveness of the evaluation in the long run, compared with the do nothing option, appears to be sound. Additionally, as only average treatment and diagnosis costs were given, it is not possible to determine what the cost of an 'average patient' entailed. The economic evaluation would have been strengthened by the use of a synthesised analysis of costs and an outcome measure such as life years gained or quality-adjusted life-years.

The authors usefully identified the factors and practices that limit the reliability of the results, such as improper collection of urine specimens, trauma due to instrumentation, improper storage and recent excessive exercise. The authors also stressed the importance of follow-up of patients without a diagnosis after evaluation – in one follow-up study, by Carson and colleagues,[1262] 16% of patients had significant lesions and 0.005% had bladder cancer.

Novicki and colleagues[269] considered the most cost-effective evaluation to adopt in assessing patients for cancer (primarily bladder cancer) who have an indeterminate outcome for urine cytology. The rationale for the study was that there is considerable doubt about how to evaluate these patients. Three strategies were adopted: (1) the evaluation of patients with a history of bladder cancer or presenting with haematuria; (2) the evaluation of patients with a history of bladder cancer, presenting with haematuria, or with a history of smoking; and (3) the evaluation of all patients with indeterminate urinary cytology. These were compared with a 'do nothing' strategy.

The perspective adopted in the economic analysis was that of the third-party payer (Medicare and non-Medicare schedules in the USA). The economic study was carried out in Arizona, USA.

The effectiveness data were derived from a retrospective cohort study using a large sample of 9763 completed cytologies, of which 675 were indeterminate and 389 also underwent a full urological evaluation. Underlying causes were determined by IVP and cystoscopy.

The incremental cost-effectiveness ratio (ICER) was calculated as the additional cost per additional case detected. The ICER for strategy 1 relative to the strategy of no evaluation was $1339 for Medicare and $4295 for non-Medicare patients. The ICER for strategy 2 relative to strategy 1 was $3376 for Medicare patients and $10,862 for non-Medicare patients. The ICER for strategy 3 relative to strategy 2 was $17,405 for Medicare patients and $55,814 for non-Medicare patients.

The study concluded that patients with indeterminate urinary cytology who are non-smokers, and have neither haematuria nor a history of urothelial cancer, are at low risk for malignancy and do not warrant complete evaluation.

The checklist score for this study was that 65% of applicable points were adequately addressed, and the matrix cell was A3, indicating that the strategies (1, 2 and 3), compared with do nothing or the next most effective strategy, require additional funding to implement.

Parekattil and colleagues[70] aimed to evaluate the diagnostic and economic outcomes of implementing a neural network of three tumour markers, compared with haematuria and cytology in screening for bladder cancer. The hypothesis of the study was that the new algorithm could result in higher sensitivity and specificity values than the two standard approaches. Unnecessary invasive procedures (cystoscopy) may also be avoided. An algorithm was created with three sets of cut-off values, modelled to be 100% sensitive for superficial bladder cancer, 100% specific for superficial bladder cancer, and 100% specific for muscle invasive cancer.

The study population comprised patients presenting to the urology clinic for cystoscopic evaluation. The economic study was carried out at the Division of Urology of the Albany Center in Albany (NY), USA. Definitive diagnoses were obtained by cystoscopy.

The effectiveness analysis showed that the diagnostic characteristics of the neural network were superior to those observed with the standard approaches (haematuria and cytology). This implies an improvement in quality of life through avoidance of invasive procedures. Cost savings were also observed in comparison with the current cancer screening protocol of haematuria and cytology. The authors stated that their model may not be applicable to all clinical settings because of the nature of the procedures and speed required to analyse the specimens.

In terms of the quality checklist, the study correctly addressed 75% of applicable items, and the hierarchical matrix result was cell G_3, which means that the costs of the tumour markers assessed are lower than the haematuria/cytology strategy and the effects more favourable.

Wakui and Shiigai[1088] explored the question of the cost-effectiveness of mass screening for urinary tract cancer using RDC compared with conventional screening. The comparator was justified as the procedure that patients would normally undergo.

The perspective was that of the Japanese Health Insurance System (JHIS) and the study population was males and females aged between 20 and 79 years who had a positive urine dipstick test, indicating the presence of occult haematuria.

RDC screening was performed at the time of haematuria-positive identification. The design of the study was a non-randomised, prospective study in which patients were followed up for 3 years from the RDC test.

The conclusions of the study were that RDC is a safe and cost-saving approach for screening patients with asymptomatic microhaematuria compared with conventional practice of full investigation. Complete urological work-up for asymptomatic microhaematuria should be restricted to those patients with normocytic or mixed haematuria, as identified by the RDC, those identified with microcytic haematuria being safe from urological cancer.

In terms of the quality checklist, the study correctly addressed 80% of applicable items, and the hierarchical matrix result was cell G_1, which means that the costs of RDC screening are lower

than the comparator of a full evaluation and the effects equivalent.

Zippe and colleagues[28] aimed to evaluate the use of an enzyme immunoassay for nuclear matrix protein in voided urine (NMP22) as a marker for the early detection of TCC of the bladder, in patients with haematuria or other indications of risk for malignancy. The sensitivity and specificity of NMP22 were compared with those of urinary cytology and the results of both tests were compared with cystoscopic findings.

The study population comprised patients with microscopic or gross haematuria or other indications for risk of bladder cancer. The study was carried out in Cleveland, Ohio, USA.

The study was a single-centred, comparative study in which urine samples were divided for NMP22 analysis and cytopathology.

It was estimated that 267 cystoscopies could be eliminated through the use of urinary NMP22. This would result in a cost saving ranging from $28,032 to $111,072 (depending on the type of insurance carrier). For the 330 patients requiring evaluation, the cost of NMP22 testing would be $6600, compared with $33,000 for cytology testing, thus producing an overall cost saving of $26,400. The use of the urinary NMP22 test in place of urinary cytology to determine whether cystoscopy is required would result in a cost saving of $54,072–137,472, and a saving of at least $3039 per diagnosis of bladder cancer.

Although there were some limitations in the cost analysis, which would weaken the generalisability of the economic data, the reliability of the effectiveness findings is likely to be reasonable as the results for each test were compared with cystoscopy plus biopsy (the reference standard of diagnosis) to determine the sensitivity and specificity of each strategy.

In terms of the quality checklist the study correctly addressed 65% of applicable items, and the hierarchical matrix result was cell G_1, which means that the costs of the intervention are lower than the comparator and the effects are equal.

Summary of included abstracts

Tieng and Seay[953] assessed algorithms for the investigation of gross/microscopic haematuria using upper urinary tract imaging modalities, specifically CT/IVP versus IVP/tomography. The study was based on the results from a retrospective analysis of 708 patients (from the Wilford Hall Medical Center and Brooke Army Medical Center in the USA), and aimed to determine the average cost and diagnostic yield of an upper urinary tract evaluation (to find significant underlying causes of haematuria) using each strategy, and the additional studies that would be required for each.

The results were 2% significant findings (1% urological) for each strategy. Additional studies were required in approximately 20% of either method but only 8% were for equivocal urological findings in the CT/IVP group. The average cost of a haematuria evaluation was $358.87 using CT/IVP compared with $164.27 for IVP/tomography.

The authors concluded that CT/IVP does not increase the diagnostic yield of significant urological pathology or decrease the overall number of additional studies required for the evaluation of equivocal findings. However, CT/IVP generates fewer follow-up studies. IVP/tomography remains the most cost-effective initial imaging for the workup of asymptomatic haematuria. This study highlights the equivocal nature of the technology used to image the upper urinary tract and is therefore important in terms of informing the modelling.

Lawrence and colleagues[863] assessed the cost-effectiveness of screening for bladder cancer using dipsticks to detect haematuria.

The study population was males aged >50 years. A model was used to compare screening using dipsticks versus no screening. Testing was conducted for 14 days and, if negative, the tests were repeated 9 months later. If positive, a full urological evaluation was undertaken.

A figure of <$50,000 per life-year (LY) gained was considered to be cost-effective. Probabilities for the model were derived from the literature and expert opinion.

A Markov model was used to determine costs and life expectancy for different stages of bladder cancer found by screening versus clinical presentation.

The results showed that the incremental cost-effectiveness of screening versus no screening was $13,491 per LY saved. The result was robust in the sensitivity analyses but was in fact sensitive to changes in assumptions regarding the length of the asymptomatic interval between the

development of detectable microscopic haematuria and usual clinical presentation. If this period is <1 year then screening remains cost-effective.

The authors concluded that screening males who are over 50 years of age is worthwhile in comparison with other screening procedures.

Assessment of published diagnostic algorithms to inform model development

The review identified 79 publications reporting diagnostic algorithms for haematuria. None of these publications reported a comparative evaluation of an algorithm. They were therefore not evaluated in the systematic review component of this report. The bibliographic details of all the identified algorithms are reported in Appendix 6. Authoritative guidelines and sources are outlined below. Prominent among these are the AUA Best Practice guidelines,[2,11] the American College of Radiology Appropriateness Criteria[231] and the National Clinical Guideline recommended for Scotland by the Scottish Intercollegiate Guidelines Network (SIGN).[3]

The AUA Best Practice algorithms for high- and low-risk patients are shown in Appendices 9 and 10, respectively. Appendix 11 gives the SIGN guidelines (which include haematuria detection, urological and nephrological pathways) and Appendix 12 provides a detailed algorithm based on consultations with the urologists and nephrologists advising the review. These algorithms are presented for comparative purposes and are not based upon evidence identified by the systematic review element of this project.

Other published algorithms were examined to determine alternative pathways and technologies. In order to facilitate a review of all identified algorithms, a minimal but inclusive structure that had a high degree of commonality among these sources was constructed. This 'generic algorithm' is outlined in *Figure 10*, with areas of uncertainty and variation (potentially suitable for inclusion in the modelling) highlighted in bold. The aim of this section is to describe each element of the algorithm and provide an overview of variations in technology use for each. The approach adopted was to examine published algorithms in order to record as many alternative modalities for each block in the generic algorithm as possible. Non-English language algorithms were also examined and any additional approaches, not represented in the English language literature, were summarised [see the section 'Non-English language algorithms' (p. 88)].

Present

The generic algorithm begins at the point 'Present' when the patient is to be assessed for haematuria. As there is currently no formal screening programme for microscopic haematuria, at least in the UK, the scenarios within which a patient will be tested are extremely varied (for example, urine screening on joining a new GP practice, urinalyses for other conditions, insurance reasons, generally 'incidental findings'). The patient may also be asymptomatic, symptomatic or have macroscopic haematuria. Whereas patients who are asymptomatic and are to be tested for haematuria will progress through all steps in the 'Present' line, those who are symptomatic or have macroscopic haematuria may be referred immediately.

The first point of referral in these cases in current UK practice is 'Urology' for a full evaluation of the upper and lower urinary tracts (principally to exclude a life-threatening malignancy).

Test for haematuria

The first step in the generic algorithm is to test for the presence of blood in the urine. This is a point of variation/uncertainty in the algorithm as there are two possibilities, namely dipstick testing using chemical reagent strips (indirect method) or microscopy, which involves physical (direct) examination of the urine under a microscope to check for and quantify the presence of RBCs. Microscopy can be undertaken by determining the number of RBCs per millilitre of urine excreted (chamber count) or direct examination of the centrifuged urinary sediment (sediment count).[20]

The most common method within the UK at the primary care level appears to be dipstick only. However, variations exist across the UK and other countries, as borne out by the opinion of the review's urologists and nephrologists and reports in the literature. The use of microscopy by sediment count to confirm a positive dipstick test is advocated in many studies[31,63,1046,1152] and by the AUA Best Practice guidelines.[20] To take into account the sometimes intermittent nature of haematuria in patients with urological malignancies, some investigators[1049] recommend two out of three positive results (>3 RBCs/hpf) from properly collected urine specimens should be used to define microscopic haematuria, although patients at high risk (smoking history,

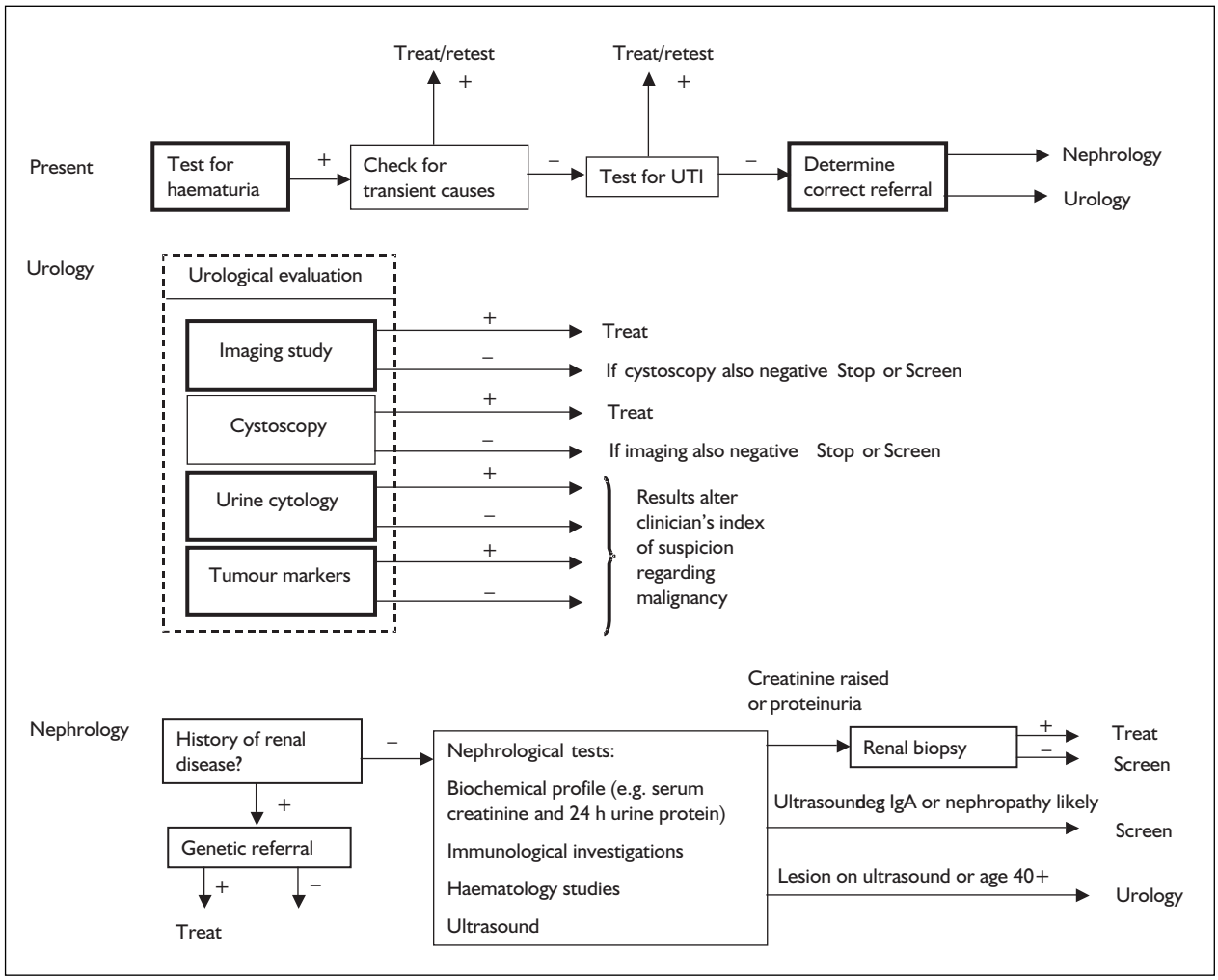


FIGURE 10 *Generic algorithm for the diagnosis of haematuria and underlying causes*

occupational exposure to chemicals or dyes, history of gross haematuria, age >40 years, history of urological disorder or disease, history of irritative voiding symptoms, history of urinary tract infection (UTI), analgesic abuse or history of pelvic irradiation) should undergo full urological evaluation after one properly performed urinalysis.[20]

Another factor for consideration is the potential variation in the accuracy of microscopy dependent upon the method adopted ('immediate' on a freshly voided sample, or 'routine' on a stored sample that is transported from primary care to a laboratory). Degradation of RBCs in stored samples may lead to an increased number of false-negative results. The choice of test and the modality used to begin the investigation are important issues to evaluate as the number of true and false cases found will have an impact on the prognosis of the patient and progression through the algorithm.

'Test for haematuria' was therefore chosen as an area to in which to undertake modelling [see the section 'Model 1 – haematuria detection (p. 93)].

Check for transient causes

The next step in the algorithm is to rule out common transient causes of haematuria.[1100] Typically these include bleeding caused by recent vigorous physical exercise, menstruation, sexual activity, viral illness and trauma.[20] The clinician would normally use the patient's medical history and the results of a physical examination to determine if the recorded haematuria is likely to be transient in nature, and may re-test for haematuria after the suspected cause has been eliminated.

Test for UTI

Once all benign causes of a positive result have been resolved, the next step is to check for a UTI. The reference standard of diagnosis is an MSU culture analysis. If a UTI is diagnosed, sensitivity analyses are undertaken as part of the culture test to determine the most appropriate antibiotic to prescribe for the patient. Once the UTI has been successfully treated, the clinician would normally test again for haematuria to ascertain if the initial positive result was caused by the UTI.

Determine correct referral

The next step in the 'Present' section of the algorithm is to determine the most appropriate referral, namely 'Urology' or 'Nephrology'. This involves a number of tests to evaluate renal function and to determine if the haematuria originates in the nephron (glomerular or tubular) or is non-glomerular (epithelial). This may be achieved through testing for the following:[20] (1) proteinuria (using a dipstick test that may be included on a multi-reagent strip used to initially test for haematuria); (2) red cell casts (microscopy); (3) serum creatinine (by blood test); (4) elevated blood pressure (BP); (5) examination of RBC morphology or volume distribution using microscopy or automated flow cytometry techniques (not commonly used in UK practice). Only one positive result among the above is usually required for a nephrology referral.

If primary renal disease is not indicated or suspected through the above, or if any of the following are present: smoking history, occupational exposure to chemicals or dyes (benzenes or aromatic amines), history of gross haematuria, age >40 years, previous urological disorder or disease, history of irritative voiding symptoms, history of recurrent UTI despite the use of appropriate use of antibiotics, then current UK guidance/practice suggests that patients should be referred to urology.

This stage of the algorithm is subject to variation, most notably in terms of who undertakes testing. In many instances, especially in the UK, tests to determine the correct referral will be undertaken by a urologist as the first point of referral from primary care. However, some GPs will undertake at least some of the above tests and consider associated risk factors before referring patients. The SIGN guidelines indicate that the primary care investigation should include detection of haematuria (microscopy ≥5 RBCs/hpf or positive dipstick test), history, examination, renal function, urine microscopy and culture).[3] For healthcare systems that are 'office' based (such as in the USA), much of the evaluation will be undertaken at the first point of contact and this may afford some advantages in terms of diagnosing haematuria, particularly with regard to the availability of immediate microscopy as opposed to routine. Potential exists to optimise referral patterns by conducting preliminary investigations in primary care. However, significant expertise is required for adequate analysis of RBC morphology or volume distributions, for example, a specially trained technician is required in a central diagnostic laboratory.[475]

A new technology, the Clinitek-50 (Bayer) urine microanalyser, suggests that economic benefits can be obtained using this technology as it conducts standard urinalysis (pH, RBCs, white blood cells, nitrite, glucose, protein, density, ketone) – normally undertaken in a laboratory and involving the transportation of urine samples.[1263] The analysis of 50 samples per week, in a study conducted by the authors, showed an annual saving of Can$40,000 compared with laboratory analysis.

Urology

Although this part of the algorithm is concerned with the detection of any underlying urological cause of haematuria, the primary concern for the urologist is to rule out life-threatening malignancies of the upper and lower urinary tracts. To do this, a suite of tests is used, within which some may be considered as possible substitutes, but others as complements. Some techniques are more effective than others in detecting particular types of tumour (or other causes) according to their location and make-up, and some modalities may not be suitable for particular patient groups such as pregnant/young women. The AUA Best Practice guidelines for urology are divided into high- and low-risk patients. Both algorithms are reproduced in Appendices 9 and 10.

Imaging studies

The first box of the urological evaluation in the generic algorithm (*Figure 10*) is 'Imaging study,' which aims to detect any neoplasms of the urinary tract, including renal cell carcinoma and the less prevalent transitional cell carcinomas of the renal pelvis and ureters, urolithiasis, cystic disease and obstructive lesions.[695] As other investigations focus attention on the lower urinary tract, imaging studies principally aim to rule out or find lesions of the upper urinary tract, although they are also, in many cases, able to detect lesions in the lower urinary tract.

The most widely established approach is IVU,[31] which includes plain abdominal X-rays of the KUB. Other alternatives and combinations that appear in diagnostic algorithms in the literature, and were considered plausible by the urologists in the review, are the following:

1. US + KUB
2. US + KUB followed by IVU for indeterminate results
3. US + KUB followed by CT for indeterminate results
4. CT alone
5. US alone
6. IVU + US
7. CT urography
8. MR urography
9. CT without contrast agent (for patients with suspected stone disease)
10. multidetector CT urography (MDCTU).

One study, included in the systematic review,[145] found that US had acceptable accuracy when compared with IVU for the detection of any abnormality associated with haematuria. US avoids the risks associated with ionising radiation and intravenous contrast media. US is also appropriate for use during pregnancy[32] and for the elderly.[1179] The initial workup of patients with microscopic haematuria should include renal US (and cystoscopy) and re-evaluation after 3 months.[528] For those with persistent haematuria and no definitive diagnosis, IVU may also be performed, although it has been shown to provide limited additional information in research on day-case haematuria services adopting US as the principal imaging study.[1179] However, US is affected by operator skill and CT may detect pathologies missed by US, such as solid tumours that are <3 cm in diameter.[1264] KUB is usually able to detect small stones of the ureter and Khadra and colleagues[14] suggested that IVU and US should be combined in order to maximise diagnostic efficiency and avoid the risk of missing upper tract neoplastic pathological conditions.

The above evidence suggests that US + KUB may be a cost-effective option.

As IVU may miss small renal masses and sometimes cannot differentiate solid from cystic masses, a follow-up study using US, CT[231] or MRI may be ordered.[695] CT is often advocated for further workup to assess operability and to ascertain the nature of detected upper tract lesions.[1179]

If the patient is suspected of having stone disease, a CT scan without contrast agent is suggested by some as being appropriate as a first test.[33] Studies using IVU or US are often followed by additional imaging (CT) to confirm that cysts are benign or to re-evaluate questionable or negative studies and, if CT is unavailable or considered to be too expensive, excretory urography, US or combinations of the two are reasonable alternatives.[695]

If the underlying cause of the observed haematuria is detected by upper tract imaging, the urologist will treat accordingly, although this would not necessarily rule out investigations of the lower urinary tract as multiple causes may be present in the patient.

Two emerging modalities, CT urography and MR urography, are described as alternative approaches by the American College of Radiology Appropriateness Criteria.[231] CT urography consists of CT of the entire urinary tract which is augmented by images of the contrast-opacified collecting systems, ureters and bladder. Although CT urography seems to be being used with increasing frequency in some settings, demonstration of its efficacy in empirical terms is incomplete.[231] MR urography, on the other hand, cannot be recommended as an initial modality as it is not commonly used in clinical practice.[231] A recent study[1016] advocates the use of MDCTU within an algorithm that initially tests for calculi without contrast medium, and in the absence of detection goes on to image using contrast medium for patients aged over 40 years. If urinary tract calculi are detected in patients under 40 years old, the investigation is terminated owing to the low likelihood of malignancy for this age group. This modality has the advantage of being able to image the whole urinary tract and offers the possibility of 'virtual cystoscopy', with sensitivities of 90% reported for bladder lesions determined by cystoscopy.[1016]

This technique appears to be replacing excretory urography as a diagnostic imaging study of choice in the USA for patients with ureteric colic or suspected urolithiasis. It is also considered the reference standard in that setting for the evaluation of the renal parenchyma for renal masses. However, before it can be considered as a universal 'one-stop' imaging test for haematuria, its diagnostic accuracy in the evaluation of urothelial neoplasms must be scientifically proven.[1016]

The AUA Best Practice guidelines indicate that evidence-based imaging guidelines cannot be

formulated because of the lack of impact data regarding IVU, US, CT and MRI modalities. IVU appears to remain the initial choice in practice but further imaging is often necessary, especially in the case of small renal masses.[20] The heterogeneity in underlying pathologies and the relative differences in diagnostic performance of imaging modalities for each of them highlight the difficulty in making optimal and cost-effective choices, based on current evidence.

Cystoscopy

The source of microscopic haematuria remains obscure in approximately 70% of cases after upper urinary tract imaging and analysis of the urine for evidence of glomerular haematuria.[695] In order to assess the lower urinary tract, cystoscopy is regarded as the reference standard procedure. There are two variations, namely flexible and rigid,[20] which can be performed under local anaesthesia, with rigid cystoscopy being associated with increased pain and post-procedure symptoms.

If gross bleeding from one ureteral orifice is discovered on cystoscopy, renal angiogram or renal venogram (imaging of kidneys following intravenous injection of contrast material) or intraluminal endoscopy might be considered.[31,1137,1147]

As cystoscopy is an invasive procedure associated with a degree of patient discomfort and slight risk of adverse reaction, some algorithms advocate the use of other tests prior to cystoscopy to refine the clinician's index of suspicion and/or limit cystoscopy to high-risk microhaematuria patients only. Alternatively, cystoscopy is suggested in some studies to be appropriate only when risk factors for bladder cancer are present[20] or in older men.[695] Evidence from the literature shows that support for cystoscopy is less in the case of women with asymptomatic microscopic haematuria.[137,321]

Urine cytology

Urine cytology is undertaken in order to investigate the presence of malignant cells in the urine, as an indicator of bladder cancer. The accuracy of cytology is regarded as variable with respect to the detection of life-threatening lesions and this is supported by the data presented in the systematic review section of this report. It is therefore used, in current practice, to modify the index of suspicion of malignancy (for example, a positive result would be highly predictive of a tumour but a negative result would not rule out performing cystoscopy). The sensitivity of cytology is higher for high-grade bladder cancer and carcinoma *in situ*, but lower with regard to the detection of low histological grade, and cytology is insensitive in the detection of renal cell cancer.[695]

Tumour markers

Tumour marker tests are an alternative or complementary method of providing evidence of bladder cancer. A report,[70] based on a double-blind RCT of 253 patients, suggests that an NMP22, monocyte chemoattractant protein-1 and urinary intercellular adhesion molecule-1 may be more accurate than haematuria and cytology in the diagnosis of bladder cancer (including muscle-invasive cancer). Research in this area is expanding and a number of markers are available (BTA, NMP22, BT *stat*, BTA Trak, Lewis X Antigen, Telomerase, FDP, Cytokeratin 20, CD 44v), with varying degrees of sensitivity and specificity in the detection of bladder cancer.[11] Only those markers where studies of diagnostic accuracy, in the context of the investigation of haematuria, were identified are included in the systematic review section of this report. However, the data presented in this section are an indication of the variability in diagnostic performance of tumour markers.

The use of voided markers is attractive as they offer the potential to avoid unnecessary cystoscopies and the more labour-intensive option of urine cytology, and therefore this part of the algorithm is a candidate area for modelling studies.

Nephrology

History of renal disease?

The first element of the 'Nephrology' algorithm (*Figure 10*) is to determine if the patient has a family history of renal disease. If this is positive, the nephrologists will make a genetic referral to determine if the patient has either familial nephritis or polycystic kidney disease (PKD).

Nephrological tests

In the final element of the 'Present' algorithm (determine correct referral) information will be available regarding whether the patient has either hypertension, proteinuria (on urinalysis), cellular casts or dysmorphic red cells. If one of these tests is positive, the patient will undergo a number of 'Nephrological tests' (*Figure 10*). This stage involves measuring (or noting the previous results in the 'Present' part of the algorithm) of (1) serum creatinine and 24-hour urine protein (biochemical profile); (2) immunological investigations [immunoglobins, antinuclear antibodies (ANA), neurophil cytoplasmic antibodies (ANCA)]; (3) US

to exclude a structural lesion of the kidney. The American College of Radiology Appropriateness Criteria also suggest that a chest X-ray be given in addition to US.[231] The results of this suite of tests would determine the next step in the algorithm.

Renal biopsy

If either creatinine is significantly raised or the patient has proteinuria, the nephrologist would normally undertake a biopsy. If the result is positive, the patient would be treated accordingly. If the result is negative, the investigation may stop or the patient followed up as considered necessary

If serum creatinine is normal and no proteinuria is detected, a urological cause becomes more likely and US is performed. If a lesion is observed, the patient will be referred to urology for assessment and treatment. Also, if the patient is over 40 years old, he or she is considered to be at increased risk of a urological disorder and again the patient will be referred to urology. However, if the result of US is negative, the most likely diagnoses are IgA nephropathy or thin membrane nephropathy. In this case, the patient will be screened annually for BP, urinalysis and serum creatinine, the results of which would determine further diagnoses/treatment.

Primary care/secondary care split

Analyses of the algorithms and discussions with the clinical experts reveals that there are questions regarding which parts of the algorithm can be undertaken in primary care and which have to be conducted in the secondary care setting. In this regard, there seems to be scope for GPs to undertake some additional tests before referral to the appropriate specialisation (urology or nephrology) as shown in the 'Determine correct referral' box of the 'Present' part of the algorithm. The tests that are applicable are those for proteinuria, erythrocyte casts, increased serum creatinine, BP (age-related), dysmorphic cells and RBC volume. It may also be cost-effective for GPs to monitor/screen patients following a negative assessment from urology, or an outcome requiring annual screening from nephrology, and where necessary provide repeat referrals.

Follow-up/screening after negative test results

For patients who have negative results after urological or nephrological investigations, as indicated in the previous section, follow-up and monitoring may be deemed appropriate. The AUA guidelines[20] suggest that, for urology, this should consist of urinalysis, BP and cytology at 6, 12, 24 and 36 months. Patients who have persistent haematuria, hypertension, proteinuria or glomerular bleeding should be evaluated for primary renal disease, those with gross haematuria, abnormal cytology or irritative voiding symptoms without infection should undergo a repeat complete evaluation and those with a negative result for 3 years should have no further urological monitoring.

Evidence from two follow-up studies[14,440] suggests that no further urological evaluations are necessary unless the patient becomes symptomatic.

In a recent UK-based study[1265] of long-term (3 years) follow-up of patients discharged from a one-stop haematuria clinic, 418 patients were evaluated using a standard protocol [MSU (microscopy, culture and sensitivity), US and KUB, history, digital rectal examination and flexible cystoscopy]. A total of 200 patients were discharged without pathology and requested to test for haematuria after 3 months, and investigated with CT if positive. Only two patients (97% response rate) were found to have underlying pathology at follow-up – one was discovered at 3 months and one had haematuria at 20 months, and was subsequently found to have a small G1pTa TCC of the bladder. The authors concluded that the algorithm used is an effective way of monitoring and investigating patients with haematuria.

Non-English language algorithms

The systematic review searches identified 33 non-English language algorithms detailing mainly diagnostic processes in other European countries. The approach adopted to capture pathways from these algorithms was to examine them in order to determine if any additional modalities were reported that were not covered in the English language papers. The following summary, therefore, is based on publications that provided additional information.

In terms of urological investigations, an Austrian algorithm[411] outlines a strict sequence of sonography, IVU and/or tomography, retrograde uretero-pyelography, rinse cytology, ureterorenoscopy and/or sample excision and, finally, optional CT or MRI. Although most of these tests are covered in the explanations for the generic algorithm, ureterorenoscopy is not, but it facilitates endoscopy of the ureter and renal pelvis. The most common indication for ureterorenoscopy is the retrieval of ureteric stones.

In a German publication,[189] steps for glomerular and non-glomerular bleeding were differentiated,

and within non-glomerular evaluation renal and post-renal haematuria arms are included in the algorithm in a similar manner to the AUA Best Practice algorithms.

Another German publication[1230] provides a detailed list of differential diagnosis possibilities, including 'beteurie' – the intake of beetroot.

One German paper[691] describes the 'three glasses' method, which requires the patient to empty their bladder using three glasses. If all the glasses are equally clouded, it is assumed that the bleeding has its source in the kidney. If the first two glasses show small amounts of blood but the third glass does not, bleeding of the bladder is likely. In a third case, where the first and third glasses but not the second glass are found to be full of blood, the bleeding is assumed to be located in the bladder base, bladder outlet, prostatic urethra or male adnexa. This paper also describes a 'bladder rinse'. If the bladder is quickly blood free and it takes a while for the rinse liquid to become red again, the authors advise that the source of the bleeding is the kidneys. If, however, the source of the bleeding is the bladder, a clear rinsing is not possible.

The German algorithm by Topf and Reuter[965] is very specific in terms of what the underlying cause of haematuria could be (i.e. urethra polyp). It also mentions the three glasses method[691] and scintigraphy as a diagnostic method, and differentiates uni- and bilateral results of the cystoscopy.

One German algorithm[694] points out that renal biopsies are only indicated in normal-sized kidneys and not in small kidneys; the algorithm proposes an arteriography to check for tumours but it is unclear when this should take place in the diagnostic sequence.

In a Swedish algorithm,[415] US, cytology and cystoscopy are fixed steps in the investigation of haematuria, whereas urography, CT, angiography and renal biopsy are explicitly depicted in an extra 'possible further investigations' box.

The search also identified a German publication that used primarily different protein markers in the investigation of haematuria and the differentiation of possible underlying causes.[396]

A Swiss algorithm[633,1239] adds a check after PCM once a non-glomerular cause of haematuria has been established to eliminate artefacts from the stomach, intestine or genital tract. The urological investigations also include a test for tuberculosis and blood clotting.

A further Swiss algorithm[1239] adds magnetic resonance tomography and flexible ureterorenoscopy as tests in the investigation of haematuria. The algorithm also makes recommendations regarding what to investigate with which method (i.e. cystoscopy for bladder and urethra mucosa and the prostate).

The following publications could not be translated and were not used to investigate incremental information: Borisov and Sura[456] (Russian), Tsoufakis and Tzanetou[1005] (Greek), Chen and Tsai[660] (Chinese), Lindell[916] (Finnish) and Prokopiuk and Wierzbicki[467] (Polish).

Limitations of the evidence to support diagnostic algorithms

Cohen and Brown[695] pointed out that data are inadequate to support clear recommendations regarding the evaluation and management of microscopic haematuria. Problems include inconsistencies in definition, study design, selection criteria, diagnostic techniques and procedures used.[750] Data are limited in terms of assessing outcomes in patients with haematuria who did not undergo an evaluation, and for those that underwent an evaluation but the underlying cause remained unexplained. Perhaps of more importance, there have been no randomised trials comparing the outcomes associated with different strategies.[695] These observations are supported by the findings of the current systematic review.

The choice of modelling questions

The above findings suggest that four areas within the generic algorithm are suitable for modelling, as indicated in *Figure 10*. These lead to four questions that could usefully be addressed:

1. What is the most cost-effective strategy to detect microscopic haematuria?
2. What is the most cost-effective strategy to determine referral (urology or nephrology) for cases of confirmed microscopic haematuria?
3. What is the most cost-effective strategy to image the urinary tract for cases of confirmed microscopic haematuria?
4. What is the most cost-effective strategy to investigate the lower urinary tract for cases of confirmed microscopic haematuria?

Owing to limitations in the available data for localisation techniques [see the section 'Localisation of the source of bleeding' (p. 33)], it was not considered reasonable to model question 2. Further justification for this decision is that the techniques to assess RBC morphology or volume distribution described in the section mentioned above are not commonly used in current UK practice. Several other indicators (e.g. hypertension, RBC casts, creatinine) may be used to inform referral decisions, for which no accuracy data were identified.

Two alternative approaches to modelling were considered. One approach would be to attempt to model patients passing through the whole algorithm and determine the overall impact on costs and clinical consequences. The second approach is to model each area of variation within the algorithm and consider the decision analytic domain as a series of unique questions that can be informed by modelling. The preferred option, many would argue, is the former, as the diagnostic process is a continuum and the progression of patients through any algorithm is dependent on what went before and what lies ahead in terms of diagnostic tests. The limiting factor in this approach, however, is the number of alternatives for each area of uncertainty and the number of unique strategies that would need to be evaluated. The diagnostic pathway for haematuria, as can be observed from the review results, is extremely complex and is associated with a number of different outcomes of interest as patients progress through the model.

In considering the number of unique strategies that would need to be evaluated using the 'joined up' approach and available effectiveness data from the review, a figure of more than 500 (four embedded decision nodes with five for haematuria detection, three for correct referral, five in upper tract imaging and seven for investigate lower tract, respectively) was calculated. An alternative approach would be to limit the number of options to be modelled at each embedded decision node, but this approach would exclude valid alternatives to be considered at each decision node and therefore present a limited set of options to a decision-maker or clinician.

It was therefore decided to present the modelling as a series of discrete questions, with the results providing an indication of what the optimal algorithm may be and some indication about what trade-offs could be applied at each point.

The second area to be considered was the question of the outcomes to use for each model. There is a strong argument for modelling health outcomes beyond cases detected, and ultimately this would be the most informative method of evaluating a diagnostic algorithm.[1266] However, as Mariani and colleagues[1049] state, "haematuria is a symptom caused by a myriad of conditions spanning the entire breadth of genitourinary pathology". In their study of 1000 patients with either microscopic or gross haematuria, the distribution of the 36 underlying pathologies was found to be renal (4.7%), renal pelvic (4%), ureteral (0.9%), bladder (19.7%), and urethral (59.2%). From evidence presented by Malström,[1028] only tumours of the bladder present with microhaematuria to an extent that it can be considered to be an early sign of the disease. The results from a Swedish study showed that only 4% of newly diagnosed bladder cancer cases had been referred solely on the basis of having microhaematuria, and 6% in a similar American study.[12]

Although modelling of the impact of bladder cancer (the most prevalent life-threatening cause of haematuria) detection with regard to long-term health outcomes and cost-effectiveness was considered, there are many other underlying pathologies that would warrant analyses in the long run. Using Miriani and colleagues' classification of causes for asymptomatic microscopic haematuria,[1049] under the classification 'Life-threatening' Grossfield and colleagues[2] cite bladder cancer, renal cell carcinoma, prostate cancer, ureteral transitional cell carcinoma, metastatic carcinoma, urethral cancer, penile cancer, renal lymphoma and abdominal aortic aneurysm as causes of haematuria. Furthermore, with regard to early signs of bladder cancer, Malström[1028] indicates that the literature provides no evidence that cancers causing only microhaematuria are less advanced at diagnosis than those causing (painless) macroscopic haematuria (the most common symptom in newly diagnosed bladder cancer patients).[147] In a study of patients reported to the American tumour registry, those who were detected by screening for haematuria did not differ from unscreened patients in relation to tumour stage or grade,[1136] or in terms of the proportions of low-grade superficial cancer as opposed to high-grade or invasive bladder cancer.[1139] Cohen and Brown[695] also point out that the US Preventive Services Task Force and the Canadian Task Force on the Periodic Health Examination do not recommend screening of urine for microscopic haematuria, cite the low predictive value of a positive screening test even in

high-risk older patients and point to the absence of proof that early detection improves the prognosis in the small number of patients found to have urinary tract cancer. The SIGN guideline also states, in this regard, that "there is no evidence that screening for microscopic haematuria is useful in any age group and no evidence that detection of disease at an earlier stage improves outcome". This is supported by evidence from follow-up studies.[440,1267] It should also be noted that studies included in this review indicated that the presence of microscopic haematuria has poor accuracy as a test for bladder cancer; see the section 'Haematuria as a test for the presence of disease' (p. 30).

In terms of evidence to show that long-term survival associated with bladder cancer is higher in those evaluated by a diagnostic algorithm compared with those who are detected in normal practice, one abstract was found[1268] showing differences in 10-year survival.

However, the evidence required to investigate one underlying condition in the long term was not forthcoming from the present study and it was considered to be both selective and problematic to attempt to choose one particular underlying cause to model. This question, along with other similar questions concerning life-threatening conditions associated with haematuria, would require separate investigations in further research.

Methods

A decision tree, incorporating the model's input parameters and strategies, was constructed using the software package Data Professional (TreeAge Software). The structure of the model was determined from the findings of the review, and consultations with the urologists, nephrologists and primary care advisors to the review concerning plausible strategies and combinations of tests. Although immediate forms of microscopy in the detection of haematuria are unlikely in the UK primary care setting, the review assumes that haematuria is an incidental finding and therefore microscopy as a first test is feasible. The aim of the model is to reflect the costs and consequences of tests in comparison with the reference standard of immediate microscopy, especially in relation to dipstick testing, and as such the alternative strategies facilitate this process.

In order to determine the efficiency of each strategy the terminal nodes (*Figure 11*) of the tree were assigned a value of either '1' or '0'. This enabled the following solutions to be calculated:

- *Mean cost per true case detected* – achieved by assigning the value '1' to a true-positive terminal node and the value '0' to false-positive, true-negative and false-negative nodes.
- *The total number of false-negative results* – achieved by assigning the value '1' to all false-negative terminal nodes and the value '0' to all other terminal nodes (as above).
- *The total number of false-positive results* – achieved by assigning the value '1' to the false-negative terminal nodes and the value '0' to all other terminal nodes (as above).

It was considered important to quantify the false-positive and false-negative values of each strategy as these provide valuable information to the clinician in addition to the cost and number of true cases detected. The implications of false-positive results within the algorithm would be further expenditure to test patients with a more reliable test, which may be associated with a degree of unnecessary morbidity for the patient (especially in undergoing cystoscopy, some forms of imaging and renal biopsy). False-positive results may also induce adverse psychological responses in patients who may question future results which show that they are negative. In the case of false-negative results the patient may have a serious or life-threatening condition that is missed, resulting in a potentially poorer prognosis following late detection. In many algorithms found in the literature and those covering current practice in the UK, patients with a negative evaluation are followed up (especially if they have associated risk factors) with repeat testing to make allowances for the potential for false-negative test results.

The probabilities after chance nodes for the model are calculated according to the standard conventions of Bayes' theorem.[1269] The essence of the calculations is that once the sensitivity and specificity of a test are known, along with the *a priori* probability of disease (prevalence), it is possible to determine the posterior probabilities of disease and absence of disease.

Accordingly, if a patient has an abnormal test result the probability of disease – the 'true-positive rate', also referred to as the 'positive predictive value' (PPV) – is represented as P(D+|T+), and if the patient has a normal test result, the probability of disease – the 'false-negative rate' – is similarly presented as P(D+|T–). These are calculated as follows:

$$P(D+|T+) = P(T+|D+)\,P(D+)/P(T+|D+)\,p(D+) + p(T+|D-)\,P(D-)$$

$$P(D+|T-) = P(T-|D+)\,P(D+)/P(T-|D+)\,P(D+) + P(T-|D-)P(D-)$$

where

$P(T+|D+)$ I = the sensitivity of the test
$P(D+)$ = prior probability of disease (prevalence)
$P(T+|D-)$ = 1 – specificity
$P(D-)$ = 1 – prevalence
$P(T-|D+)$ = false-negative ratio
$P(T-|D-)$ = true-negative ratio.

Where two tests are connected in series, the calculations are the same except that the prior probability of disease (prevalence) for the second test is the calculated 'true positive rate' of the first test.

To illustrate in the construction and analysis of the haematuria tree (*Figure 11*), consider the strategy 'dipstick followed by immediate microscopy'. The probability of a test positive result following dipstick, pPos_D = (Se_D**a priori*) + (1 – Sp_D)*(1 – *a priori*), where Se_D = sensitivity of the dipstick test, Sp_D = specificity of the dipstick test and *a priori* is the prevalence for patients before the test. From this, the probability of a negative result is 1 – pPos_D.

The probability of a positive result for microscopy following a positive dipstick result, pPos_D_IM = (Se_IM*pPPV_D) + (1–Sp_IM)*(1–pPPV_D), where Se_IM = sensitivity of immediate microscopy, Sp_IM = specificity of immediate microscopy and pPPV_D = positive predictive value of the dipstick test = (Se_D**a priori*)/pPos_D.

The positive predictive value for immediate microscopy following a positive dipstick result in pPPV_DIM = (Se_IM*pPPV_D)/pPos_D_IM.

The negative predictive value of immediate microscopy is similarly calculated as pNPV_DIM = [Sp_IM*(1 – pPPV_D)]/(1 – pPos_D_IM), and the negative predictive value after a negative result for dipstick is pNPV_D = [Sp_D*(1 – *a priori*)]/(1 – pPos_D).

All probabilities in the remaining strategies in the tree are calculated in a similar manner.

Costs

Calculations of total cost for each strategy are determined using recursive costing, available with Data Professional. This is achieved by setting the cost variable = 0 at the root node. As the tree expands from left to right, the 'cost' variable is modified by adding new cost variables to the variable 'cost'. In this way, the value of 'cost' at each terminal node is unique to the path from the root node to that terminal node. In the example strategy being used, 'dipstick followed by immediate microscopy,' 'cost' = 'cost + cost_D' after the dipstick test, 'cost + cost_IM' after microscopy for positive results from the dipstick test and 'cost + cost_C' after a positive result for immediate microscopy. The value of 'cost' at the 'true-positive' terminal node is therefore the cost of dipstick, microscopy and consultation with the GP.

Prevalence

As the prevalence of haematuria varies considerably among different subpopulations, three values were used in the base case solutions: prevalence in young adults (0.39%) and prevalence in a high-risk group of serious underlying cause of haematuria (males over 50 years of age), which has been shown to be of the order of 10–21%. By modelling three prevalence levels (0.39, 10 and 21%), an indication of the relative cost-effectiveness of assessing each subgroup could be determined, which also provides useful information regarding the relative effectiveness and cost-effectiveness of evaluating different subgroups.

The results are provided in the form of mean outcomes and costs, from which dominated strategies (those with lower effectiveness and higher costs) can be eliminated. ICERs are then provided for strategies that remain. The model was probabilistic in that suitable distributions were assigned to each variable where this was feasible.

Sensitivity analysis

Uncertainty in the model's parameters was assessed by probabilistic sensitivity analysis (PSA) using second-order Monte Carlo simulations, which provided a mean, standard deviation and CI for the model's estimates that are assigned a distribution. As the raw data from the review were available, either as part of a pooled (weighted) mean or from a single study, one possibility for the distribution of sensitivity and specificity variables was the *beta* distribution as this is bounded between zero and one and requires three available estimates (*alpha*, *beta* and scale). *Alpha* is defined as the number of events observed in a sample and *beta* the number of non-events in the same sample. Scale is determined from the two other estimates.

Therefore, in the calculation of sensitivity, alpha is the number of true positives recorded and beta the number of false negatives; for specificity distributions, *alpha* denotes the number of true-negative results and beta the number of false-positive results.

However, initial testing with *beta* distributions revealed that distributions with a large scale were too tight around the mean and did not adequately represent the wide variation in the pooled data. Therefore, random effects meta-analyses to pool the raw data, with estimates produced on the log-odds scale, were chosen.[1270] This approach has recently been applied to a diagnostic algorithm[1271] and initial testing produced variations in the results more consistent with the data. Within the model, these parameters are incorporated as normal distributions, with the transformed (sampled) log values being converted by means of the formula

exponential(parameter[log distribution])/
(1 + exponential)(parameter[log distribution]))

During Monte Carlo simulations, values for sensitivity and specificity are randomly sampled from these distributions and an expected value (costs and effects) is calculated for each iteration – the final result being an average of all iterations (in this case 10,000).

The model was tested using a hypothetical population of 1000 patients who were to be evaluated for haematuria for a wide variety of reasons, principally based on incidental findings and not part of an organised screening programme. The choice of 1000 patients was based on an estimate (JKe) of the number of patients evaluated for haematuria each year in a typical UK Trust.

Results are provided in tables, cost-effectiveness planes (which show the magnitude and direction of costs and effects), scatter plots (to represent graphically the results of the probabilistic sensitivity analyses) and cost-effectiveness acceptability curves (CEACs) (which depict the probability of a decision being cost-effective for a range of willingness to pay (λ) values) as appropriate for the results.

Model 1 – haematuria detection

The first major element of diagnostic algorithms is the detection of microscopic haematuria itself. This was considered to be appropriate for modelling as there is uncertainty concerning the most appropriate test or combination of tests to use,[900] or whether testing for microscopic haematuria in adults should be conducted at all.[1028] The aim of this first model was therefore to determine the most cost-effective strategy to use, ruling out the 'do nothing' option, by taking into account the diagnostic accuracy and costs associated with each test. The results of the review of diagnostic algorithms show that there are three generic approaches to the detection of microscopic haematuria:

- dipstick testing
- microscopy (routine)
- microscopy (immediate).

These tests can be used as independent tests or used to confirm the results of an initial test. The structure and rationale of the model are described in the following.

Dipstick is an indirect, low-cost method in which tests are either single reagent tests or multi-reagent strips that detect blood and protein in the urine. They are potentially useful, as the detection of proteinuria is an element for determining whether referral to a nephrologist in diagnostic algorithms for haematuria is necessary. The use of dipsticks in primary care is by far the most common first test undertaken in the UK.

Although dipstick testing provides a rapid and simple method of detecting blood in urine,[1046] doctors are usually reluctant to accept the results of dipstick tests alone without confirmation using microscopy.[544] It is also common practice for clinicians to request MSU culture (to rule out UTI) on the same urine sample following an initial positive test for haematuria. Unlike dipstick testing, microscopy has the potential to serve more than one purpose. More detailed microscopic analyses may be used to determine the referral of patients with microscopic haematuria and a degree of overlap therefore exists with the 'determine correct referral' decision. In this scenario, however, only the issue of haematuria detection is considered.

Microscopy can be performed using a number of different approaches. The most common method is centrifuged/sediment analysis,[900] but chamber count methods are also available. Inverted phase microscopy is also sometimes used and may be more useful in the analysis of urine for dysmorphic RBCs. The presence of dysmorphic RBCs is used to indicate a referral to nephrology.

Microscopy is assumed in the model to be the reference standard for detecting haematuria. However, its performance may be adversely affected by sample degradation. RBCs are not stable in urine and lysis during storage and transportation of samples is likely to lead to a significant increase in the number of false-negative results observed. This issue gives rise to the distinction made between the accuracy of 'immediate' and 'routine' microscopy.[900] Immediate is taken to be analysis conducted on a freshly voided sample within a short space of time at the same premises (less than 2 hours in the study by Dowell and Britton[900]). Routine microscopy involves samples being transported to a hospital laboratory in a sterile container with boric acid to prevent bacterial growth. Usually there is one collection per day and the delay in reaching the laboratory after voiding is between 2 and 6 hours. Together with unavoidable agitation of the specimens in transit, this can result in considerable red cell lysis.[1083]

The above appraisal led to the view that five strategies should be used to evaluate the cost-effectiveness of haematuria detection:

1. Dipstick alone – use dipstick (practice nurse). Consultation with GP if positive and specialist referral (if other causes, including infection, are eliminated). Stop if dipstick test is negative.
2. Microscopy (routine) – Take urine sample from patient in the GP surgery and send to Trust/laboratory for microscopy without doing initial dipstick test. If positive, referral to urologist (if other causes eliminated).
3. Microscopy (immediate) – suspect patient may have haematuria, therefore refer directly to a specialist or screening centre to give urine sample and have microscopy immediately.
4. Dipstick followed by routine microscopy if positive – use dipstick (practice nurse). If positive send urine sample to Trust/laboratory for microscopy. If positive, consultation with GP and specialist referral if other causes have been eliminated.
5. Dipstick followed by immediate microscopy if positive – use dipstick (practice nurse). If positive, send patient to a specialist or screening centre for microscopy. If positive, consultation with GP and specialist referral if other causes have been eliminated.

Associated with all of the above strategies are a number of caveats in that the GP will take into consideration a number of factors before referring the patient to a specialist department. These include consideration of the patient's medical history, age, whether the patient is at high risk of a serious underlying cause of haematuria and whether other transient explanations can be found, such as recent vigorous exercise or menstruation. The model is shown graphically in *Figure 11*.

The underlying assumptions of the model are as follows:

- A positive test result for any strategy would result in a referral for further investigation of the underlying cause of microscopic haematuria.
- Costs would include both those incurred in the administration of tests and associated consultations, plus those associated with false results.
- In the case of a false-negative result, it is assumed that the patient will return for an additional test for microscopic haematuria and costs to reflect this were added to the false-negative branches of the tree.
- False-positive results incurred additional (unnecessary) costs downstream at the next point in the algorithm (determine correct referral). In this case, the cost was assumed to be further microscopy. This is a conservative estimate as patients with false-positive results may proceed through a full urological evaluation as the 'determine correct referral' using more accurate localisation analyses are not standard practice in the UK setting.

Model input parameters

In order to populate the model for each strategy, it was necessary to obtain suitable test performance, epidemiological and cost data. The sensitivity and specificity of the dipstick test as well as 'immediate' microscopy were determined from the findings of the review. The review identified no sensitivity and specificity data for routine microscopy. In order to overcome this limitation, an estimate was made by clinicians and those with relevant laboratory experience who were advising the review. It was considered that sensitivity would be the test parameter most likely to be affected and a value of 0.5 was chosen based on a 50% reduction in performance compared with the reference standard. The specificity of routine microscopy was considered to be less affected by sample degradation and a reduction of 20% in performance was considered to be plausible, giving a value of 0.8. These values were used as point estimates to which plausible ranges were attached: 0.4–0.6 for sensitivity and 0.7–0.9 for specificity. These were applied to the model.

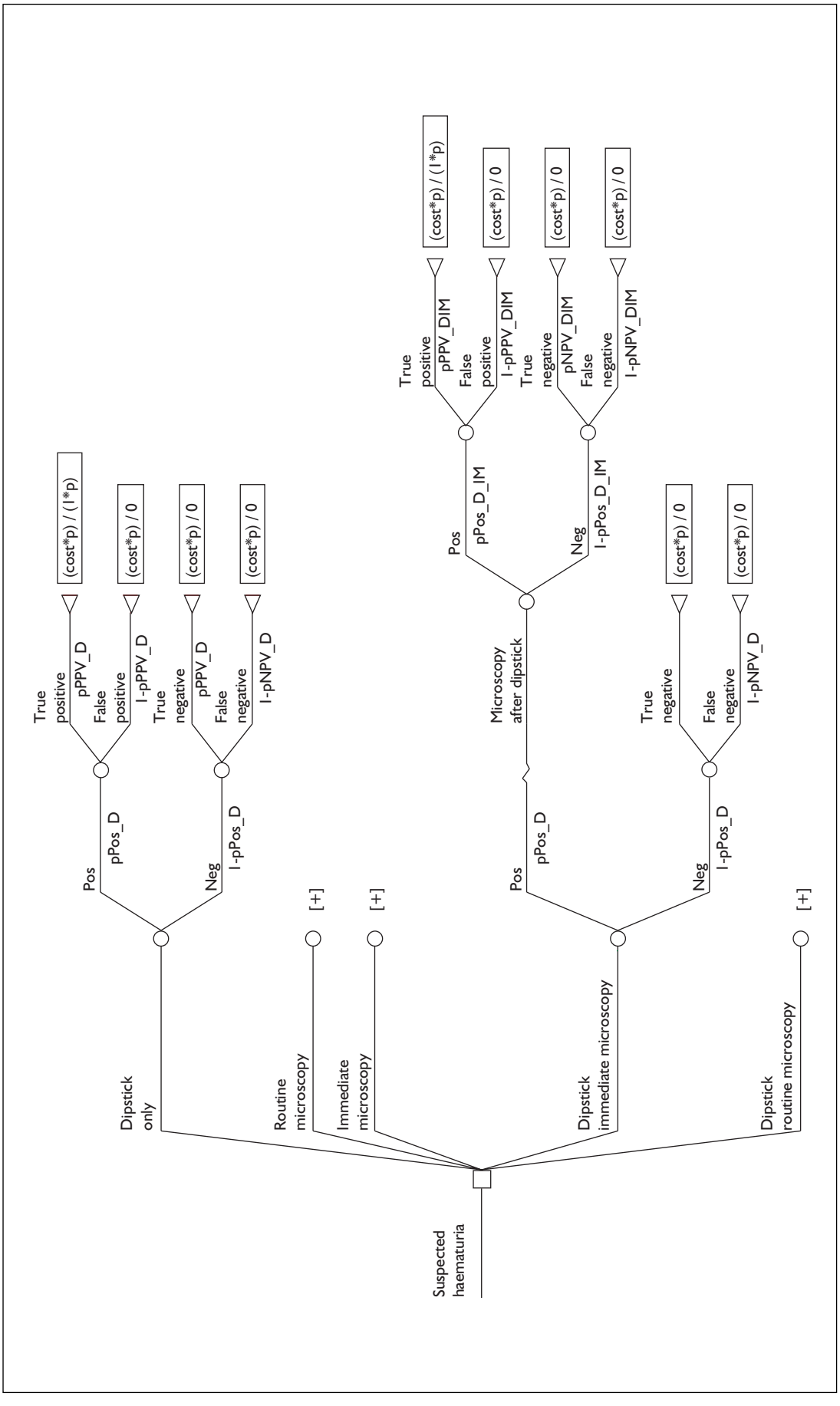


FIGURE 11 *Decision tree for microscopic haematuria detection. Strategies marked [+] are identical with one of the two strategies shown*

TABLE 23 *Test performance and epidemiological data for haematuria model*

	Parameter				
Test	**Log odds**	**Standard error**	**Distribution**	**Mean (range)**	**Source**
Dipstick					
Sensitivity	1.588	0.145	Normal	0.97	Review[49–52,54–56,58–67]
Specificity	1.761	0.245	Normal	0.75	Review[49–52,54–56,58–67]
Immediate microscopy					
Sensitivity			Fixed	1	Reference standard
Specificity			Fixed	1	Reference standard
Routine microscopy					
Sensitivity			Uniform	0.5 (0.4–0.6)	Panel estimate
Specificity			Uniform	0.8 (0.7–0.9)	Panel estimate
Prevalence					
Young adults			Fixed	0.39%	Topham (2004)[977]
Males >50, high estimate			Fixed	10%	Messing (1987)[63]
Males >50, low estimate			Fixed	21%	Messing (1987)[63]

Epidemiological data, in this case the prevalence of microscopic haematuria in subpopulations of interest, were also required. These were derived from the studies included in the systematic review. The details of each parameter, along with sources, are provided in *Table 23*.

Costs associated with each test were required, taking the perspective of the UK NHS. The source of the cost data was either the NHS Reference costs (2003 data), Personal Social Services Research Unit (PSSRU) (2003 data) or York Hospitals NHS Trust (2004 data; Booth A: personal communication). All cost data were then inflated to a price year of 2004.

In some cases, estimates were made in the absence of reliable or specific data for each test – for example, an additional cost of £5 was estimated to cover the cost of transporting urine samples for strategies that included routine microscopy, and for initial microscopy a value of £54.80 was used under the NHS Reference category of 'minor pathology test' in urology. The cost of further microscopy, assumed to involve more sophisticated techniques, was assumed to be £92.37 (in 2004 data). This is the cost of an 'intermediate pathology test' in urology.

The BNF did not provide details of the cost of dipstick testing for haematuria. Data from a UK supplier were therefore used. These are a very low-cost item (£0.08) and were very similar to other dipstick cost data provided in the BNF. Full details of the cost data are shown in *Table 24*.

Model results

Table 25 shows the baseline results for each strategy in terms of mean values for cost, incremental cost (Incr cost), effectiveness in terms of true cases detected (Eff), incremental effect (Incr Eff), average cost-effectiveness ratio (C/E), ICER, false-positive rate (FP) and false-negative rate (FN). Strategies are listed in ascending order according to cost.

The results are reported in a stratified manner according to the three prevalence levels chosen for the analysis. For clarity, in terms of interpreting the baseline (mean) results, the results are also shown on the cost-effectiveness plane of *Figure 12*.

For all prevalence levels the 'immediate microscopy' strategy is the most effective strategy (detecting all cases) and is less costly than the 'routine microscopy' strategy, which involves a large number of false results that generate extra costs.

For a prevalence value of 21%, the results show that the strategies 'routine microscopy,' 'dipstick followed by routine microscopy,' 'and 'dipstick followed by immediate microscopy' are dominated. In other words, they are more costly and less effective than one of the two remaining strategies, 'dipstick alone' and 'immediate microscopy.' The incremental cost-effectiveness is £816 per additional case detected by moving from 'dipstick alone' to 'immediate microscopy'. As the prevalence drops to 10 and 3.9%, the 'dipstick followed by immediate microscopy' strategy

TABLE 24 *Cost data for haematuria model*

Resource	Quantity	Value (£)	Source	Distribution
Dipstick				
Practice nurse	1	9.20	PSSRU	Fixed
Dipstick[a]	1	0.08	UK supplier	Fixed
Microscopy (immediate)[b]	1	54.8	NHS reference costs	Fixed
Microscopy (routine)	1	54.8	NHS reference costs	Fixed
Transport (to laboratory)	1	5	Estimate	Fixed
GP consultation	1	18.27	PSSRU	Fixed
Repeat testing (false negatives)	1	82.35	NHS reference costs	Fixed
Further investigation (false positives)[c]	1	92.37	NHS reference costs	Fixed

PSSRU, Personal Social Services Research Unit (www.PSSRU.ac.uk).
[a] URS-5K supplied by Access Diagnostic Tests UK (tests for blood, protein, glucose, ketone, pH and protein).
[b] Microscopy is based on the cost of a 'minor pathology test' (L13op Urology HRG).
[c] Additional microscopy is assumed to involve localisation techniques and is based on an 'intermediate pathology test' (L14op, Urology HRG).

TABLE 25 *Cost-effectiveness results for haematuria model (for abbreviations, see text)*

Strategy[a]	Cost (£)	Incr Cost (£)	Eff	Incr Eff	C/E (£)	ICER (£)	FP	FN
Prevalence = 0.39%								
Dipstick immediate microscopy	19,798		32		619		0	7
Dipstick routine microscopy	*24,844*	*5,046*	*16*	*–16*	1,553	*Dominated*	*29*	*23*
Dipstick only	26,139	*6,341*	32	*0*	817	Dominated	145	7
Immediate microscopy	54,713	*34,915*	39	*7*	1,403	4,988	0	0
Routine microscopy	*82,030*	*27,317*	*19*	*–20*	4,317	*Dominated*	*191*	*19*
Prevalence = 10%								
Dipstick immediate microscopy	23,854		83		287		0	17
Dipstick only	26,982	*3,128*	83	*0*	325	Dominated	135	17
Dipstick routine microscopy	*30,622*	*6,768*	*41*	*–42*	747	*Dominated*	*27*	*58*
Immediate microscopy	55,827	*31,973*	100	*17*	558	1,881	0	0
Routine microscopy	*84,269*	*28,442*	*19*	*–81*	4,435	*Dominated*	*179*	*50*
Prevalence = 21%								
Dipstick only	28,444		174		163		118	36
Dipstick immediate microscopy	31,137	*2,693*	174	*0*	179	Dominated	0	36
Dipstick routine microscopy	*40,804*	*12,360*	*87*	*–87*	469	*Dominated*	*24*	*123*
Immediate microscopy	57,837	*29,393*	210	*36*	275	816	0	0
Routine microscopy	*86,901*	*29,064*	*105*	*–105*	828	*Dominated*	*159*	*105*

[a] Strategies containing routine microscopy (shown in italics) are based on estimates of sensitivity and specificity by the review's expert panel.

becomes less costly and as effective as dipstick alone. The incremental cost-effectiveness at a prevalence of 10% increases to £1881 per additional case detected, and at 3.9% to £4988 (in relation to 'immediate microscopy').

Table 25 shows that the highest number of false-negative results is produced by 'dipstick routine microscopy' followed by 'routine microscopy.' As the prevalence level increases, strategies that commence with dipstick also produce high numbers of false-negative results (36 at a prevalence level of 21%). In terms of serious underlying causes being missed, these strategies should be of prime concern as they are more likely to be associated with health-related losses.

Dipstick testing is associated with high numbers of false-positive results (for example, 118 at a prevalence level of 21%). This could lead to a high number of patients undergoing further (unnecessary) evaluations. This could have resource implications in light of the UK '2-week rule', which states that microhaematuria detected

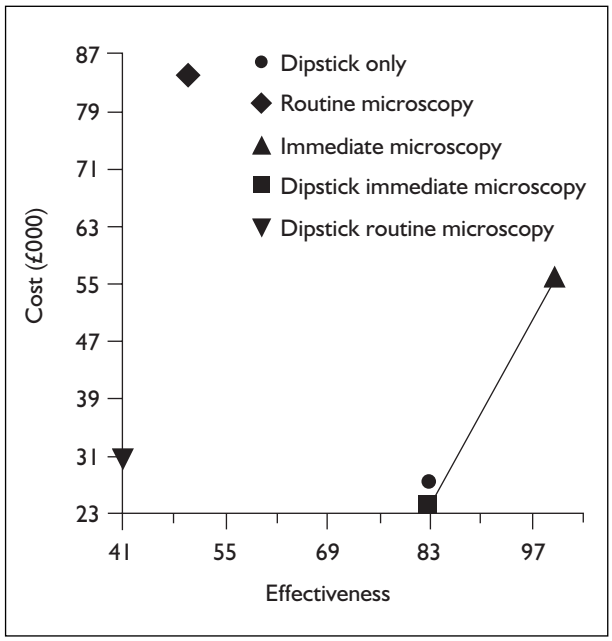


FIGURE 12 *Cost-effectiveness plane for haematuria model (prevalence of 10%), The line between dipstick plus immediate microscopy and immediate microscopy represents the efficiency frontier of the diagram (strategies to the left being dominated by one of the two strategies at the ends of the line)*

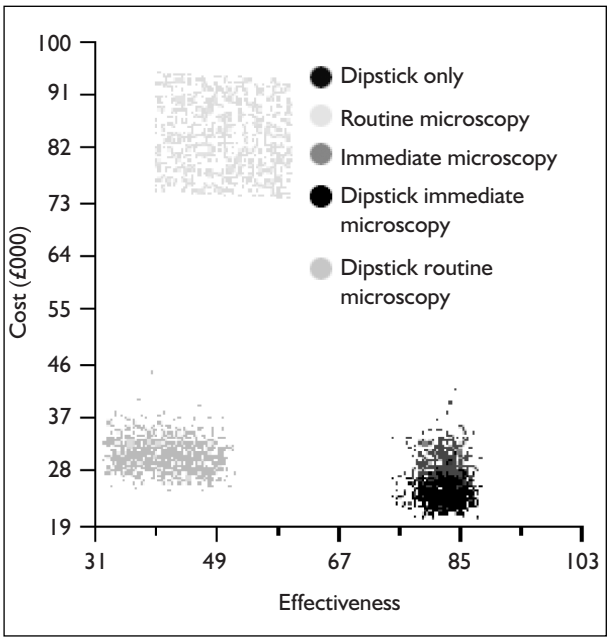


FIGURE 13 *Scatter plot for probabilistic sensitivity analysis (prevalence = 10%)*

in patients aged over 50 years should be further investigated.

The 'dipstick immediate microscopy' strategy eliminates all false-positive results and therefore makes this strategy attractive as it is less costly at prevalence levels of 3.9 and 10%, and only £2693 more costly for the evaluation of 1000 patients at a prevalence of 21%.

The findings indicate that at higher prevalence levels, decision-makers and clinicians should be more willing to use immediate microscopy over strategies that commence with dipstick testing as the relative cost-effectiveness improves.

Sensitivity analysis

The results of the probabilistic sensitivity analysis are shown in overview in the cost-effectiveness scatter plot in *Figure 13*.

The graph shows that 'routine microscopy' (top left cloud) is always more expensive and less effective than 'immediate microscopy' and is therefore always dominated. Similarly, the strategy 'dipstick routine microscopy' (bottom left cloud) is always less effective and more costly than 'dipstick immediate microscopy,' and always less effective than 'dipstick only' (partially dominated).

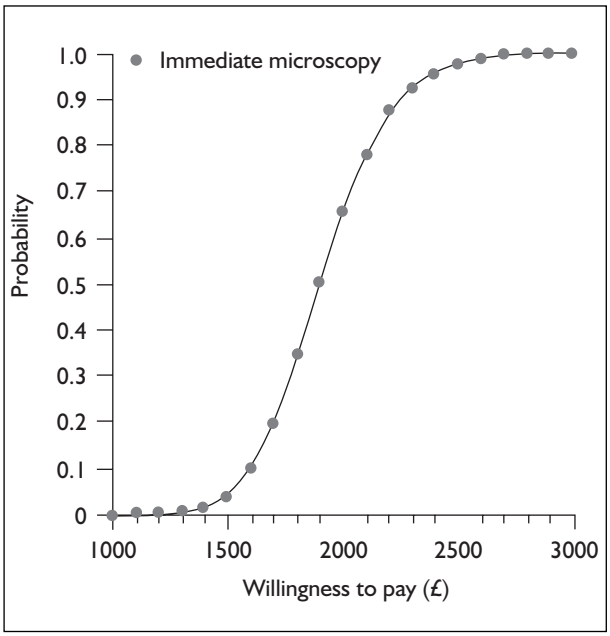


FIGURE 14 *CEAC for immediate microscopy versus dipstick immediate microscopy*

'Dipstick only' and 'dipstick immediate microscopy' have very similar dispersions for effectiveness, but 'dipstick immediate microscopy' is shown to be mostly less expensive than 'dipstick only'. The decision-maker would therefore be interested in the uncertainty in moving from 'dipstick immediate microscopy' to 'immediate microscopy.' This uncertainty is presented in the CEAC in *Figure 14*.

The graphs show the probability of the intervention being cost-effective (ordinate) for a range of willingness to pay values for a decision-maker.

The interpretation of the CEAC is that if the decision-maker is willing to pay an additional £1000 to detect an additional instance of haematuria, the probability that 'immediate microscopy' will be cost-effective is 0. On the other hand, if a decision-maker is willing to pay an additional £3000 to detect an additional case, the probability that 'immediate microscopy' will be cost-effective is 1. At a willingness to pay of £1900 (the mean ICER), the probability that 'immediate microscopy' will be cost-effective is approximately 0.5.

Model 2 – imaging of the upper urinary tract

The modelling for image upper urinary tract investigates, based on available test accuracy data from the systematic review, two decision analytic scenarios:

1. The cost per case detected for any cause of microscopic haematuria, without the benefit of follow-up screening, using the following test strategies:
   (a) US alone
   (b) IVU alone
   (c) IVU and US together
   (d) CT alone.
2. The cost per case detected for any cause of microscopic haematuria plus screening for negative results, with those with persistent haematuria receiving a more accurate test (except CT), as represented by the following strategies:
   (a) US followed by CT
   (b) US followed by IVU
   (c) IVU followed by CT
   (d) US and IVU together followed by CT
   (e) CT alone.

In the follow-up model, the structure is as shown in *Figure 15*.

The model assumptions are:

1. After an initial positive test, patients would proceed to further investigations, with the false-positive arm being attributed the cost of an additional, unnecessary test (in this case the cost of a biopsy).
2. Patients who test negative on the initial test would be screened in primary care for haematuria. For those with persistent haematuria a further, more reliable test would be given (at a later date, resulting in a delay).
3. Persistent haematuria was assumed to be present in only the false negative patients, as illustrated in *Figure 15*.

All models calculate the costs and cases detected for each strategy and indicate the additional cases and costs associated with the addition of screening.

Model input parameters

Test performance and epidemiological data used in the models are shown in *Table 26*. Cost data are shown in *Table 27*.

Both models are probabilistic and employ log-normal distributions, as described in the section 'Method' (p. 91), for all sensitivity and specificity variables.

The models were tested using a hypothetical cohort of 1000 patients and prevalence data according to three risk categories, low (3.4%), medium (30%) and high (48%), as derived from single studies included in the review and shown in *Table 25*.

Results

The baseline mean results for imaging any cause, with and without screening as derived from the Monte Carlo simulations and stratified for prevalence, are shown in *Table 28*.

Strategies are ranked in order of cost from least expensive to most expensive and show cost, incremental cost (Incr Cost), effectiveness (Eff) (cases detected) incremental effectiveness (Incr Eff), the average cost-effectiveness ratio of each strategy (C/E), the ICER, the false-positive rate (FP) and the false-negative rate (FN).

Imaging results without follow-up

The baseline results for imaging without follow-up screening and testing are represented graphically in *Figure 16*. Together with the results in *Table 28*, they show that for the detection of any cause of haematuria, CT is the most effective strategy (detecting all cases) at a total cost of £333,491 (prevalence = 30%).

Two strategies, IVU and US + IVU, are dominated by other strategies in that they are more costly and less effective than either CT or US. US detects 275 cases at a cost of £85,026 in

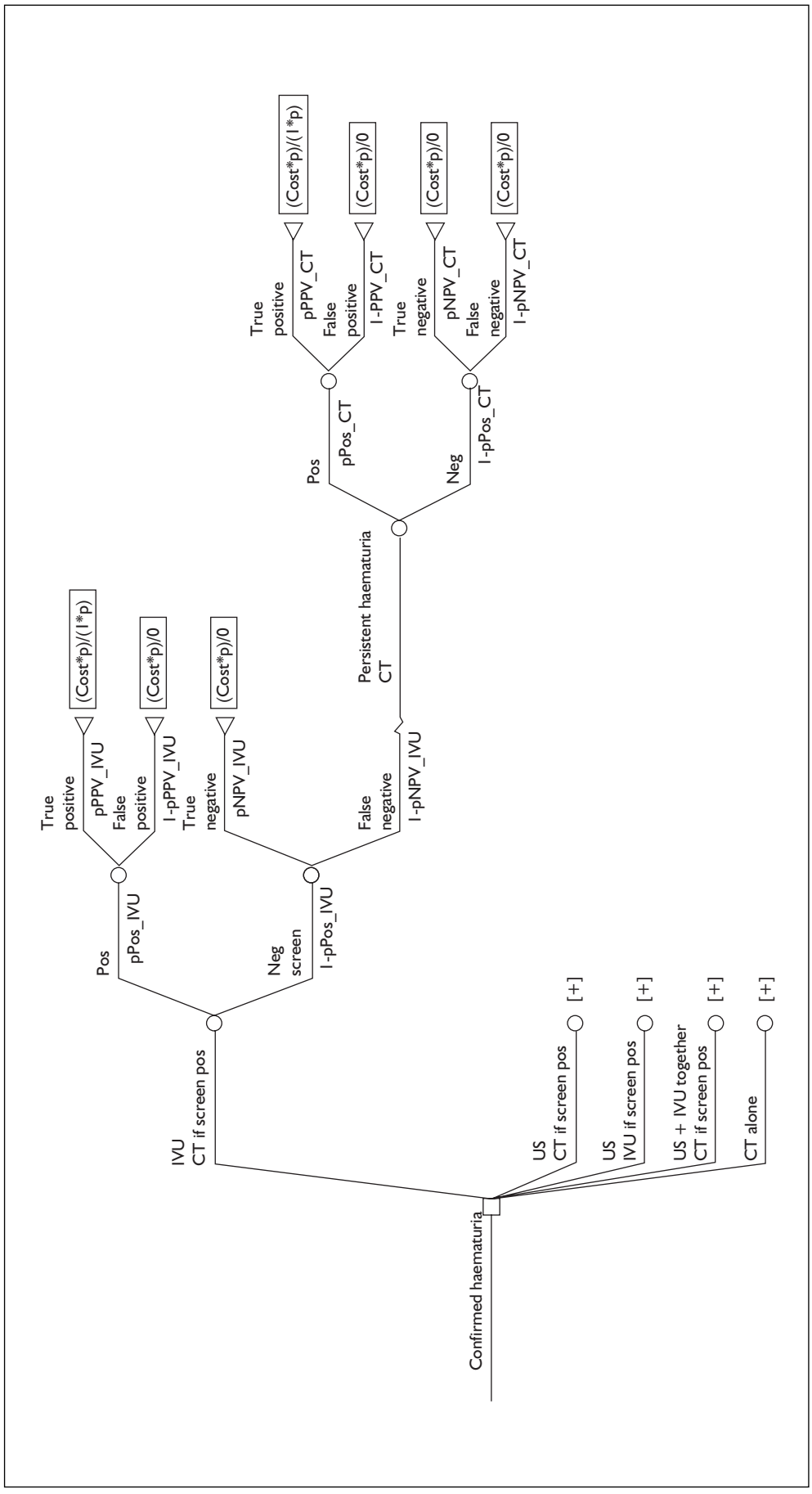


FIGURE 15 *Model structure for imaging strategies that include screening. Strategies marked [+] are collapsed. The expanded strategy is IVU followed by CT scan if negative for IVU with persistent haematuria during screening.*

TABLE 26 *Test performance and epidemiological data for upper tract imaging model*

	Parameter				
Test	**Log odds**	**Standard error**	**Distribution**	**Mean (range)**	**Source**
CT					
Sensitivity	4.344	1.423	Normal	1.00	Gray Sears (2004)[126]
Specificity	2.934	0.224	Normal	0.97	Gray Sears (2004)[126]
IVU					
Sensitivity	0.427	0.332	Normal	0.61	Gray Sears (2004)[126]
Specificity	2.303	0.396	Normal	0.91	Gray Sears (2004)[126]
US					
Sensitivity	2.393	0.428	Normal	0.92	Review[145,146]
Specificity	2.608	0.392	Normal	0.93	Review[145,146]
US/IVU					
Sensitivity	1.253	0.8	Normal	0.78	Speelman (2004)[144]
Specificity	1.978	0.18	Normal	0.88	Speelman (2004)[144]
Prevalence					
Low risk		Fixed	3.40%	Grossfeld[2]	
Medium risk (pooled)			Fixed	30%	Review[126,144–146]
High risk			Fixed	48%	Grossfeld[2]

TABLE 27 *Cost data for upper tract imaging model*

Resource	**Quantity**	**Value (£)**	**Source**	**Distribution**
CT scan	1	325	York District Trust	Fixed
Ultrasound	1	73	York District Trust	Fixed
IVU	1	267	York District Trust	Fixed
Repeat testing (false negatives)	1	309	York District Trust	Fixed
Further investigation (false positives)	1	236	York District Trust	Fixed

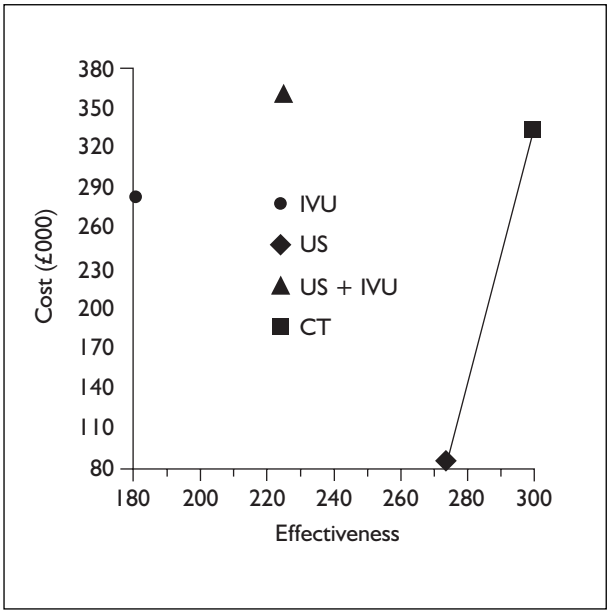


FIGURE 16 *Cost-effectiveness plane for image upper urinary tract (any cause) without screening and follow-up testing, from Monte Carlo simulation*

the baseline solution, whereas US + IVU detects 233 cases and IVU 182 cases at a much higher cost than either IVU or US + IVU.

IVU has the highest number of false-negative results (68), whereas US + IVU produces 76 false negatives. Apart from CT (no false negatives), US produces the lowest number of false negatives (27). As CT alone does not have a perfect specificity, it produces some false-positive results (36), followed by US (50), IVU (68) and US + IVU (86).

Similar trends are observed for other prevalence levels. However, the relative cost-effectiveness of CT versus US improves with increasing prevalence (£87,091 at 3.4%, £9939 at 30% and £5796 at 48%).

Results of probabilistic sensitivity analysis

The results of the probabilistic sensitivity analysis revealed the level of uncertainty concerning the

TABLE 28 *Cost-effectiveness results for upper tract imaging models, with and without follow-up screening and testing (for abbreviations, see text)*

Strategy	Cost (£)	Incr Cost (£)	Eff	Incr Eff	C/E (£)	ICER (£)	FP	FN
Baseline results for image upper tract (any cause) prevalence = 3.4%								
US	89,801		31		2,897		66	3
IVU	289,171	199,370	21	–10	13,770	Dominated	88	13
CT	336,675	248,000	34	3	9,902	87,091	49	0
US + IVU	367,960	31,285	26	–8	14,152	Dominated	117	8
Baseline results for image upper tract (any cause) with follow-up and prevalence = 3.4%								
US then IVU (screen +)	90,773		33		317		36	11
US then CT (screen +)	91,035	262	34	1	314	262	36	0
IVU then CT (screen +)	294,084	203,311	34	0	1,096	Dominated	47	0
CT alone	336,811	246,038	34	0	1,112	Dominated	26	0
US + IVU then CT (screen +)	371,408	280,635	34	0	1,288	Dominated	63	0
Baseline results for image upper tract (any cause) prevalence = 30%								
US	85,026		275		307		50	27
IVU	282,763	197,737	182	–93	1,553	Dominated	68	119
CT	333,491	248,465	300	25	1,111	9,939	36	0
US + IVU	360,410	26,919	233	–67	1,543	Dominated	86	76
Baseline results for image upper tract (any cause) with follow-up and prevalence = 30%								
US then IVU (screen +)	93,334		290		322		48	11
US then CT (screen +)	95,617	2,283	300	10	319	228	48	0
IVU then CT (screen +)	329,631	236,297	300	0	1,099	Dominated	64	0
CT alone	333,523	240,189	300	0	1,112	Dominated	36	0
US + IVU then CT (screen +)	389,221	295,887	300	0	1,297	Dominated	85	0
Baseline results for image upper tract (any cause) prevalence = 48%								
US	82,078		437		188		38	43
IVU	278,841	196,763	289	–148	965	Dominated	51	194
CT	331,299	249,221	480	43	690	£5,796	27	0
US + IVU	355,028	23,729	360	–120	986	Dominated	64	124
Baseline results for image upper tract (any cause) with follow-up and prevalence = 48%								
US then IVU (screen +)	95,421		463		206		38	17
US then CT (screen +)	99,167	3,746	480	17	207	220	38	0
IVU then CT (screen +)	352,959	253,792	480	0	735	Dominated	50	0
CT alone	331,283	232,116	480	0	690	Dominated	27	0
US + IVU then CT (screen +)	402,337	303,170	480	0	838	Dominated	64	0

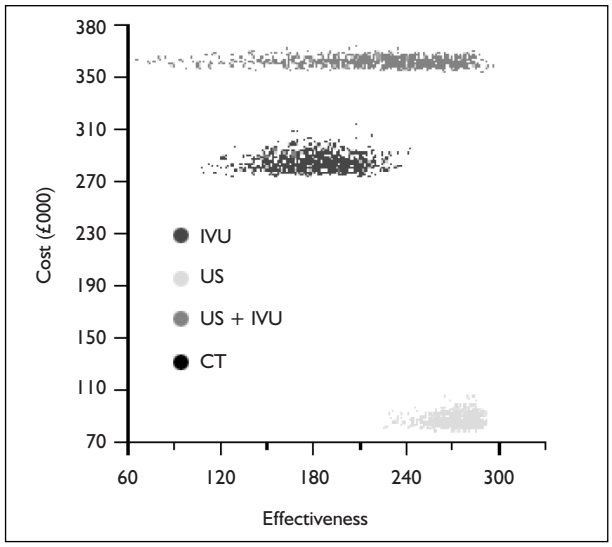


FIGURE 17 *Cost-effectiveness scatter plot for imaging without follow-up*

result, as illustrated in the scatter plot in *Figure 17*.

The strategy US and IVU (top cloud) is associated with the highest cost for all sampling and the widest variation in cases detected, and is always dominated by CT alone. Similarly, US (bottom right cloud) is always less costly and more effective than IVU and as such the most relevant alternatives, in terms of incremental cost-effectiveness and the uncertainty associated with moving from one to the other, are US and CT. This uncertainty is depicted in the CEAC in *Figure 18*.

The interpretation of the CEAC is that if a decision-maker were willing to pay £30,000 per additional (any cause) case detected, the probability that the choice is cost-effective would

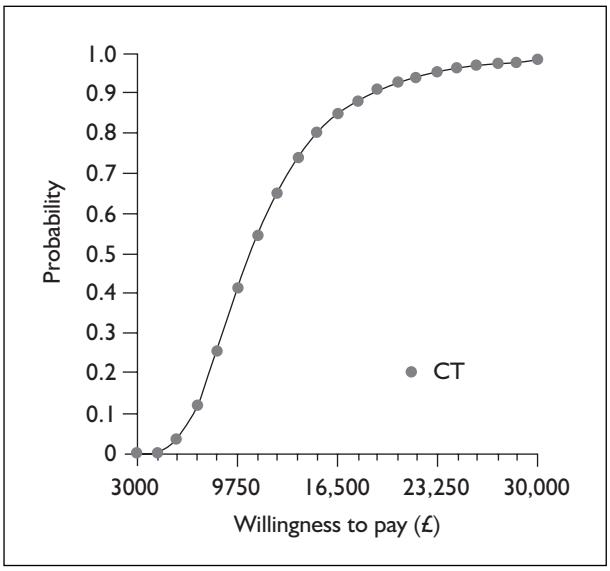


FIGURE 18 *CEAC for US versus CT*

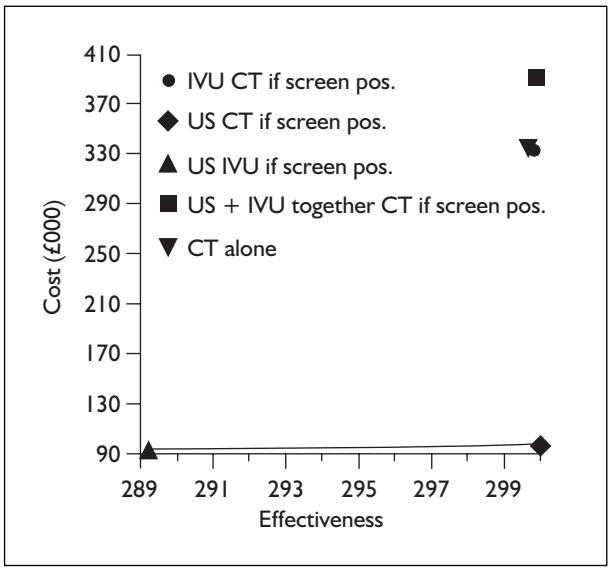


FIGURE 19 *Cost-effectiveness plane for imaging with follow-up testing, from Monte Carlo simulation*

be 1. However, if the threshold chosen by the decision-maker were only £15,000 the probability of the intervention being below this figure is approximately 0.8.

Although data are not presented in detail, the strategies US and IVU were compared in relation to tumour detection as sensitivity and specificity were available from the review. The results showed that US is the dominant strategy over IVU in that it is more effective (71 versus 67 cases detected for IVU) and less costly (approximately £90,000 versus £290,000 for 1000 patients). In terms of false results, US also dominates IVU in that both false negatives and false positives are lower. However, the effectiveness results showed that US (range 56–75) does not always detect more cases than IVU (52–74) and therefore caution must be exercised when concluding that US is the optimal choice. Data were not available from the review to assess CT and US + IVU.

Imaging results with follow-up

The results regarding costs and cases detected when screening and further imaging for screen positive patients are summarised in *Figure 19*.

From this graph, it can be seen that only the US followed by IVU strategy fails to detect all cases, and US followed by CT is the dominant strategy. In terms of false results (for example, at prevalence = 30%), US and IVU followed by CT produced the most false-positive values (85), followed by IVU then CT (64), and US then IVU (48), and CT (36). All strategies ending in CT had no false negatives, and US followed by IVU produced 11 false negatives.

Results of probabilistic sensitivity analysis

Examination of the scatter plot produced by the probabilistic sensitivity analysis showed that US followed by CT is always as effective as the other strategies in detecting all cases, and remains the least costly under all scenarios. As such it remains the dominant strategy.

The question of whether or not a delay in diagnosis would affect health outcomes and quality of life by the missing of cases in the initial imaging would need to be fully evaluated before the above finding could be validated.

Model 3 – investigation of the lower urinary tract

The 'investigate lower urinary tract' model examines the question of whether patients with microscopic haematuria defined as 'low risk' can undergo a limited evaluation (not currently universal practice in the UK but advocated in some algorithms such as the AUA guidelines[20]). In this situation, cystoscopy would only be undertaken if other tests for malignancy are positive. The nine strategies investigated without the effects of screening being added, based on data availability from the systematic review, were as follows:

TABLE 29 *Test performance and epidemiological data for investigate lower urinary tract model*

	Parameter				
Test	**Log odds**	**Standard error**	**Distribution**	**Mean (range)**	**Source**
Cystoscopy					
Sensitivity	0.427	0.332	Normal	1	Gold standard
Specificity	2.303	0.396	Normal	1	Gold standard
Virtual cystoscopy					
Sensitivity	3.02	0.724	Normal	0.953	Kim (2002)[128]
Specificity	2.639	0.732	Normal	0.933	Kim (200)[128]
Cystosonography					
Sensitivity	1.792	0.764	Normal	0.86	Cronan (1982)[124]
Specificity	3.32	0.59	Normal	0.965	Cronan (1982)[124]
NMP22 marker					
Sensitivity	1.288	0.346	Normal	0.782	Review[29,134,135,138,140]
Specificity	1.138	0.194	Normal	0.777	Review[29,134,135,138,140]
BTA marker					
Sensitivity	1.119	0.346	Normal	0.73	Review[123,129,141,148]
Specificity	1.039	0.527	Normal	0.74	Review[123,129,141,148]
FISH marker					
Sensitivity	0.754	0.303	Normal	0.68	Sarosdy (2004)[143]
Specificity	1.389	0.124	Normal	0.8	Sarosdy (2004)[143]
MCM5					
Sensitivity	1.93	0.356	Normal	0.87	Stoeber (2002)[840]
Specificity	1.925	0.181	Normal	0.87	Stoeber (2002)[840]
Cytology					
Sensitivity	1.253	0.8	Normal	0.41	Review[29,121,123,127,129, 132,134–137,140,141,143,147,148]
Specificity	1.978	0.18	Normal	0.97	Review[29,121,123,127,129, 132,134–137,140,141,143,147,148]
Prevalence					
Low risk (pooled)			Fixed	8%	Review[29,121,123,127,129, 132,134–137,140,141,143,147,148]

1. Cystoscopy alone (reference standard).
2. Urine cytology then cystoscopy if positive, otherwise screen patients every 3 months for 1 year.
3. Tumour marker (NMP22) then cystoscopy if positive, otherwise screen patients every 3 months for 1 year.
4. Tumour marker (BTA) then cystoscopy if positive, otherwise screen patients every 3 months for 1 year.
5. Tumour marker [Minichromosome Maintenance 5 protein (MCM5)] then cystoscopy if positive, otherwise screen patients every 3 months for 1 year
6. Virtual cystoscopy then cystoscopy if positive, otherwise screen patients every 3 months for 1 year.
7. Cystosonography then cystoscopy if positive, otherwise screen patients every 3 months for 1 year.

Consistent with the methods of the imaging model [see the section 'Model 1 – haematuria detection' (p. 93)], follow-up screening was evaluated by adding cystoscopy to strategies 2–7 above for negative results, assumed to be persistent for microscopic haematuria (assumed for false-negative results).

This permitted the examination of results at the initial investigation in comparison with those determined after screening positive with (delayed) cystoscopy.

Model input parameters

Effectiveness and epidemiological data used in the model are shown in *Table 29*. Cost data are shown in *Table 30*.

Results

Table 31 provides details of the cost, incremental cost (Incr Cost), effectiveness (Eff), incremental

TABLE 30 *Cost data for investigate lower urinary tract model*[a]

Resource	Quantity	Value (£)	Source	Distribution
Cystoscopy	1	671.93	NHS reference costs	Fixed
Virtual cystoscopy	1	600	Estimate	Fixed
Cystosonography	1	250	Estimate	Fixed
NMP22 marker	1	54.8	NHS reference costs	Fixed
BTA marker	1	54.8	NHS reference costs	Fixed
FISH marker	1	54.8	NHS reference costs	Fixed
MCM5 marker	1	54.8	NHS reference costs	Fixed
Cytology	1	92.37	NHS reference costs	Fixed
Specialist consultation	1	68	NHS reference costs	Fixed
Further investigation (false positive)	1	671.93	NHS reference costs	Fixed
Cost of screening				
GP consultation/BP	4	73.08	PSSRU	Fixed
Dipstick	4	0.34	UK supplier	Fixed

[a] Tumour marker costs are based on the cost of a 'minor pathology test' (L13op Urology HRG); cystoscopy is based on the cost of an intermediate pathology test (L11op Urology HRG); dipstick testing is based on URS-5K supplied by Access Diagnostic Tests UK (tests for blood, protein, glucose, ketone, pH and protein).

TABLE 31 *Cost-effectiveness results for investigate lower tract without follow-up screening and cystoscopy (for abbreviations, see text)*

Strategy	Cost (£)	Incr Cost (£)	Eff	Incr Eff	C/E (£)	ICER (£)	FP	FN
Cytology cystoscopy	272,000		40		6,800		0	40
MCM5 cystoscopy	317,000	45,000	70	30	4,529	1,500	0	10
FISH cystoscopy	352,000	35,000	54	–16	6,519	Dominated	0	26
NMP22 cystoscopy	384,000	67,000	62	–8	6,194	Dominated	0	17
BTA cystoscopy	394,000	77,000	60	–10	6,567	Dominated	0	18
Cystosonography cystoscopy	454,000	137,000	67	–3	6,776	Dominated	0	11
Cystoscopy alone	807,000	491,000	80	10	10,088	49,000	0	0
Virtual cystoscopy cystoscopy	828,000	21,000	75	–5	11,040	Dominated	0	4

effect (Incr Eff), average cost-effectiveness ratio (C/E), ICER, false positive rate (FP) and false negative rate (FN) for each strategy.

The cost-effectiveness plane for the above findings is provided in *Figure 20*.

The results show that 'cystoscopy alone' detects all 80 cases at a cost of £807,000. The least costly (£270,000) and also the least effective (40 cases) strategy is 'cytology cystoscopy'. The other strategy on the efficiency frontier of *Figure 16* is 'MCM5 cystoscopy'. MCM5 is the best performing tumour marker. All strategies to the left of the line in *Figure 20* are dominated (less effective and more costly) than either 'MCM5 microscopy' or 'cystoscopy alone'. The results perhaps explain the normal practice adopted by urologists of using both tumour marker(s) and cytology, as cytology alone misses (in this model) half the cases.

In terms of false-negative results, the worst strategy is 'cytology followed by cystoscopy' (40), with 'FISH followed by cystoscopy' (26), 'BTA followed by cystoscopy' (18), 'NMP22 followed by cystoscopy' (17), 'cystosonography followed by cystoscopy' (11), 'MCM5 followed by cystoscopy' (10) and 'virtual cystoscopy followed by cystoscopy' (4). Cystoscopy alone produces no false results.

There are no false-positive results as cystoscopy has a sensitivity and specificity of 1.

Results of probabilistic sensitivity analysis

The uncertainty in the results can be observed visually in the scatter plot in *Figure 21*. The strategy 'virtual cystoscopy' (top cloud) is always dominated by 'cystoscopy alone,' whereas MCM5 (bottom-right cloud) is always more effective than 'cytology cystoscopy' (bottom-left cloud), although this strategy is always the least expensive. Under some combinations of samples the strategy

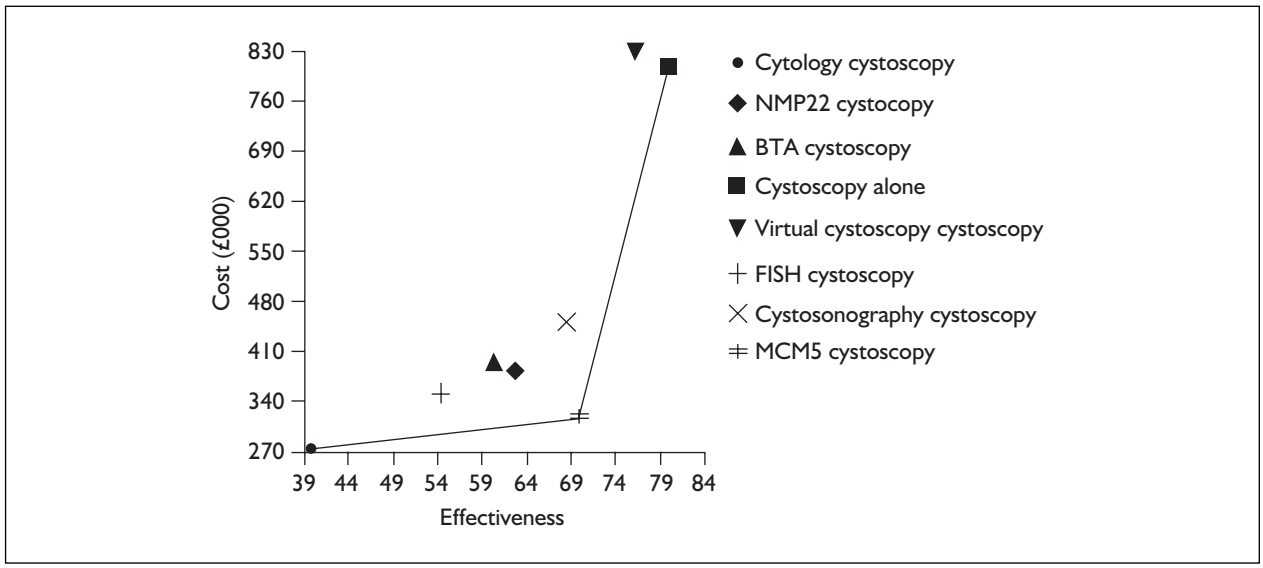


FIGURE 20 *Cost-effectiveness plane for investigate lower tract model*

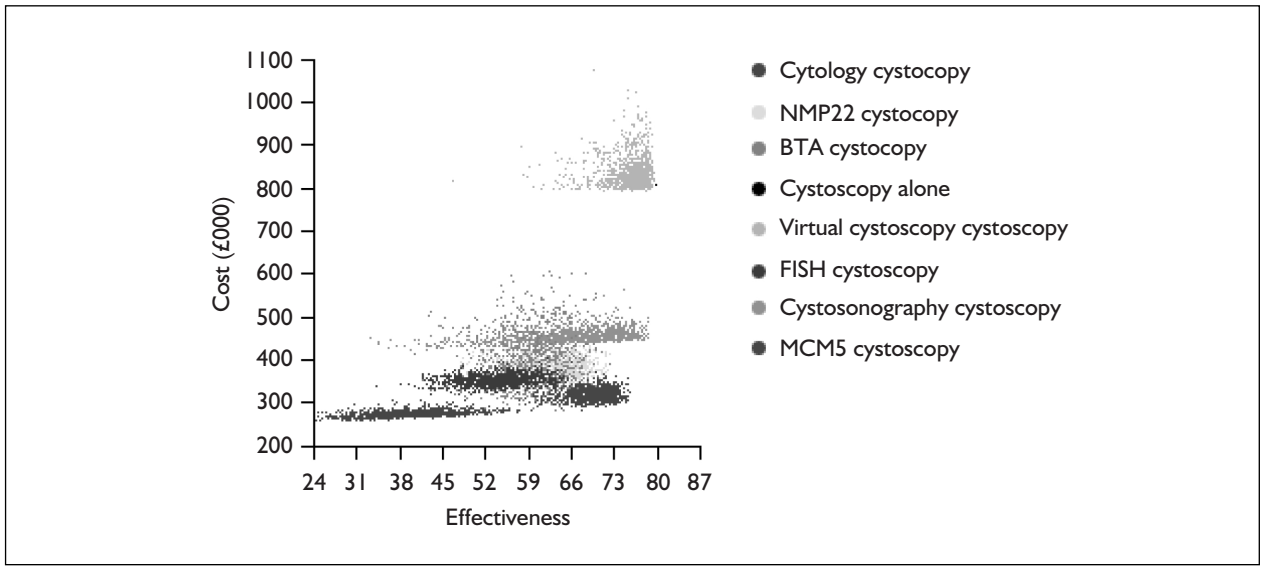


FIGURE 21 *Cost-effectiveness scatter plot for investigate lower tract without follow-up*

'cystosonography cystoscopy' becomes more effective than MCM5 as it extends to the right of the MCM5 distribution.

As cystosonography is not used in current clinical practice in the UK (but could potentially be in the future), the uncertainty in the decision along the efficiency frontier, namely from 'MCM5 cystoscopy' to 'cystoscopy alone' is represented in the CEAC in *Figure 22*. The interpretation of the CEAC is that for a willingness to pay (λ) of approximately £90,000 per additional case detected, the probability of the intervention being cost-effective is 1. For a λ of £20,000 the probability is 0, and at the mean incremental cost-effectiveness (£49,000) the probability of the intervention being cost-effective is approximately 0.6.

The impact of cystoscopy after follow-up screening

The performance of the above strategies was assessed according to the methods described for the imaging model [see the section 'Model 2 – imaging of the upper urinary track (p. 99) and *Figure 15*]. Again, those with a negative test were screened and the false negatives among this group assumed to exhibit persistent haematuria and be referred for further investigation (cystoscopy). The results are shown in *Table 32*.

TABLE 32 *Results for investigate lower tract with follow-up screening and cystoscopy (for abbreviations, see the text)*

Strategy	Cost (£)	Incr Cost (£)	Eff	Incr Eff	C/E (£)	ICER (£)	FP	FN	95% CI (Cost)
Cytology cystoscopy Cystoscopy for screen positive	301,000		80		3,763		0	0	293 to 318
MCM5 cystoscopy Cystoscopy for screen positive	324,000	23,000	80	0	4,050	Dominated	0	0	303 to 353
FISH cystoscopy Cystoscopy for screen positive	371,000	47,000	80	0	4,638	Dominated	0	0	346 to 397
NMP22 cystoscopy Cystoscopy for screen positive	397,000	72,000	80	0	4,963	Dominated	0	0	359 to 448
BTA cystoscopy Cystoscopy for screen positive	408,000	84,000	80	0	5,100	Dominated	0	0	314 to 559
Cystosonography cystoscopy Cystoscopy for screen positive	462,000	138,000	80	0	5,775	Dominated	0	0	448 to 505
Cystoscopy alone Undefined investigation screen positive	807,000	483,000	80	0	10,088	Dominated	0	0	NA
Virtual cystoscopy cystoscopy Cystoscopy for screen positive	831,000	24,000	80	0	10,388	Dominated	0	0	800 to 993

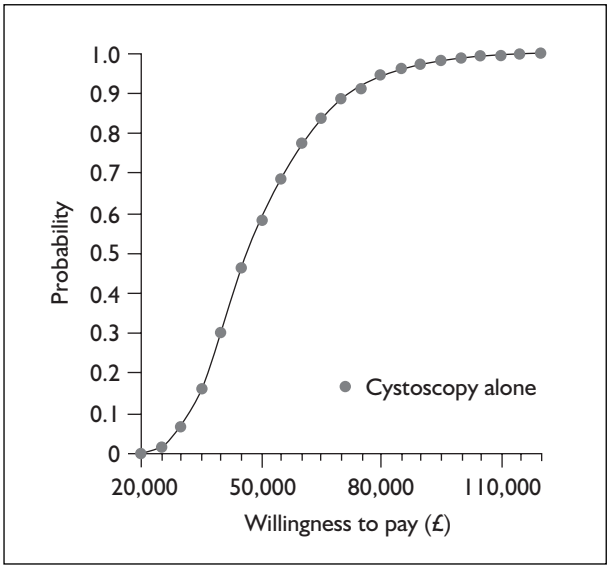


FIGURE 22 *CEAC for imaging without follow-up*

All strategies detect all of the 80 original cases. The point of interest is therefore the range of costs associated with each strategy, as determined from the probabilistic sensitivity analysis. The results show that although 'cytology cystoscopy' is the least costly, the 95% CI (£293,000 to 318,000) extends into the' MCM5 cystoscopy' strategy (£303,000 to 353,000) and there are permutations that would switch the order of the least costly strategy.

Again, the question of whether or not a delay in diagnosis for low-risk patients with a tumour of the lower urinary tract would affect health outcomes and quality of life, by the missing of cases in the initial investigations, would need to be fully evaluated before the above finding could be considered for clinical practice. Discussions with the urologists advising the review (JKe, TA) indicate that a delay of 3 months or more could affect the prognosis of a patient with transitional cell carcinoma of the bladder, whereas some other forms of bladder cancer may not progress as quickly.

Current clinical practice suggests that all patients referred for urological investigation will undergo cystoscopy, and that tumour markers and cytology are used only to adjust the urologist's index of suspicion. The AUA guidelines suggest that patients at low risk need not undergo cystoscopy immediately if they are negative for cytology (see Appendix 10). If this decision were applied in a UK context, there would clearly be an economic benefit, but there would remain a probability, albeit low, that cases could be missed with negative health and economic consequences.

Chapter 8
Discussion

This chapter is divided into two main sections, the first covering methodological issues associated with the literature review and economic modelling and the second covering the findings of the review.

Review methodology

The search strategy was developed to maximise sensitivity. This approach results in the retrieval of large numbers of non-relevant citations for screening, as was the case in this review. The time cost of this strategy is justified by the established difficulty in identifying diagnostic accuracy studies owing to deficiencies in specific indexing terms and their use.[1272]

The possibility of publication bias remains a potential problem for all systematic reviews. The extent to which publication bias is an issue for diagnostic accuracy studies remains unclear. For intervention studies there is a clear cut-off defining a 'positive result', i.e. whether there is a significant difference in outcome between the treatment and control, and whether this difference favours the intervention. This is not the case for studies of diagnostic accuracy, which are essentially a measure of agreement between the results of the index test and a reference standard. It is possible, and indeed likely, that studies reporting higher estimates of test performance will more often be published, but the extent to which this occurs is unclear. There is evidence that publication bias is a particular problem for studies of small sample size, although these data are not specific to the diagnostic literature.[1273,1274] With the aim of reducing the impact of higher levels of publication bias in smaller studies, this review excluded studies with less than 20 participants. Future work exploring the impact of publication bias in diagnostic accuracy studies would be useful in determining the extent to which this approach is valid.

The protocol for this project stated that the methodological quality of included studies would be assessed using checklists specific to study design. This is important for achieving an accurate picture of study quality. All included studies were diagnostic accuracy studies and these were assessed using QUADAS. Individual components of methodological quality, specific to diagnostic accuracy studies, could therefore be assessed using criteria developed by an evidence-based method.[1275] Methodological quality was not used to select studies for inclusion in analyses, and no summary quality scores were employed. Summary scores, when used to inform quality-based analyses, may mask important effects of individual quality components.[1276] We therefore advocate that components of quality assessment should be reported fully, and their impact on outcome measures analysed individually rather than as summary scores. However, where studies are poorly reported, the information that may be derived from quality assessment becomes limited. It cannot be known whether an unreported QUADAS item reflects a true methodological flaw or poor reporting of a study that may be methodologically sound. Many of the studies included in this review were poorly reported. The assessment of the impact of components of methodological quality on diagnostic accuracy may therefore partially reflect reporting quality. While poor reporting remains a widespread problem, it is almost impossible to assess the impact of components of methodological quality on the results of systematic reviews of diagnostic tests. The STARD initiative has provided clear guidance for the reporting of diagnostic accuracy studies[1277,1278] and its uptake should improve all aspects of the evaluation of diagnostic accuracy. Although this was a large review, with 110 diagnostic accuracy studies reporting 239 data sets, analysis of the impact of methodological quality on diagnostic accuracy was severely limited both by the diversity of the included studies (few tests were evaluated by sufficient studies to allow meaningful use of meta-analytic pooling and investigation of heterogeneity) and by the quality of reporting.

Sensitivity, specificity and LRs were used to summarise estimates of test performance. Ranges in sensitivity and specificity were reported and results of individual studies plotted in ROC space. ROC plots provide an easy to interpret visual summary of all the studies included in a review. They enable the reader to assess quickly the

variability between studies, the accuracy of the test and whether there appears to be a threshold effect, without the potentially misleading effect of pooling using a summary ROC where there is significant, unexplained between-study heterogeneity. Summary ROC curves were therefore used only to investigate potential sources of heterogeneity. LRs were used as the primary effect measure as these are the measure that physicians find easiest to interpret.[1279] Pooled LRs were presented alongside ranges where pooling was deemed clinically meaningful. The main limitation of this approach was the presence of considerable between-study heterogeneity; it is debatable whether it is appropriate to pool LRs under these circumstances. It is therefore particularly important that pooled estimates are interpreted with caution and that the heterogeneity between studies is considered when interpreting these results. A more general problem with pooled LRs as summary measures is that positive and negative LRs are pooled individually. These measures are likely to be correlated within an individual study and ignoring this correlation may be problematic. This is an area of current research in the methodology of diagnostic meta-analysis.

Regression analysis was used to investigate possible explanations for the observed heterogeneity. This analysis was conducted according to standard methods for pooling studies of diagnostic accuracy using the summary ROC approach.[44] In this, DOR is the dependent variable. The DOR is used as a single indicator of overall test performance and shows how much more often a positive test result occurs in a person with the condition of interest than in one without the condition. Using the DOR to investigate heterogeneity means that we cannot assess whether the factors investigated are associated with one or both components of paired measures of diagnostic accuracy, such as sensitivity and specificity, or positive and negative LRs. Often factors that lead to an increase in sensitivity will lead to a decrease in specificity and vice versa. Factors that lead to this pattern of change may have no effect on an overall measure such as the DOR. Using the DOR to investigate heterogeneity may therefore miss relevant clinical associations. Recent work describes a new method for pooling sensitivity and specificity. This method is known as the 'bivariate model'.[1280] It preserves the underlying two-dimensional nature of the data and produces direct, pooled estimates of sensitivity and specificity, incorporating any correlation that might exist between these two measures. The model can be extended to include explanatory variables leading to separate effects on sensitivity and specificity. Evaluation of this method may improve future insight into the impact of elements of methodological quality and other sources of heterogeneity on the performance of diagnostic tests.

Results of review

Six main objectives were identified for this project, three of which could be partially realised and three of which could not be addressed owing to a lack of relevant data.

The three objectives that could not be addressed were all concerned with the efficacy of diagnostic tests or testing strategies.

The primary aim of this project was to determine the most effective diagnostic strategy for the investigation of haematuria. In order to inform the development of a diagnostic algorithm and areas for decision analytic modelling, evidence on the effectiveness of existing algorithms was sought. Although 79 different diagnostic algorithms for the investigation of haematuria were identified, none of these have been formally evaluated (i.e. in terms of a measure of their impact on patient outcomes).

No trial evidence was identified relating to the effectiveness of screening for haematuria in either general or specific targeted populations. It should also be noted that trial evidence of the effectiveness of screening programmes forms only one component of the UK Screening Committee Criteria. Haematuria is not, in itself, a clinical condition with major health implications, but rather a symptom. In the context of screening criteria, it is therefore more appropriate to regard the presence of haematuria as a test with the theoretical potential to be used in screening for a range of target conditions, rather than as a target for screening. The studies identified in this review indicate that the simple detection of microhaematuria cannot be considered a useful stand-alone diagnostic test for the presence of significant underlying pathology (urinary calculi or bladder cancer). Although a single study reported a specificity of macrohaematuria as a test for bladder cancer of 99%[72] (indicating that macrohaematuria is of value in ruling in a diagnosis of bladder cancer in patients where other suspicious factors exist), the comprehensive evaluation of haematuria as a potential screening

test falls considerably outside the scope of this review.

A further objective was to evaluate the efficacy of investigations to determine the underlying cause of haematuria, in terms of patient outcomes. For any condition, diagnostic testing is only appropriate where the result will affect patient management and where treatments are available that will improve outcome. The effectiveness of diagnostic testing can be evaluated either directly, in the context of an RCT of a particular test versus an alternative or no test, or indirectly by combining test accuracy data with effectiveness data for available treatment(s). No RCTs of the effectiveness of further investigation of haematuria were identified in this review; therefore, to estimate the relative 'effectiveness' of these techniques on the available evidence, diagnostic accuracy data would need to be combined with estimates of effectiveness for the appropriate range of treatment options. Similarly, no studies looked at the impact of referral-based single versus repeated positive dipstick findings (the AUA guidelines suggest that a single positive dipstick is insufficient). The possibility of a relationship between timely intervention and the effectiveness of treatment is also likely to be a relevant consideration; optimising the diagnostic strategy should reduce the time to diagnosis. Investigation of the effectiveness of treatment strategies for conditions associated with haematuria was, however, outside the scope of this review.

The majority of empirical evidence identified in this review was concerned with the diagnostic accuracy of tests used to detect haematuria and to investigate its underlying causes. Haematuria is most frequently detected in the primary and secondary care settings using a reagent strip (or 'dipstick') test, and this is reflected by the fact that most of the existing diagnostic accuracy studies in this area are concerned with the accuracy of dipsticks. The main question of interest here is whether a positive dipstick result represents a true finding of haematuria. For these dipstick studies, taking the pooled positive and negative LRs alone would suggest that there is reasonable, but not overwhelming, evidence that the method is useful in establishing the presence of haematuria. The exact utility of a dipstick test is likely to depend considerably upon the clinical context in which the test is conducted and the clinicians' estimate of the pre-test probability of haematuria as a symptom of the suspected diagnosis for the particular patient. In addition, the worth of these pooled estimates is questionable, given the marked clinical and statistical heterogeneity between the existing dipstick studies. Although the included studies evaluated a number of different dipstick brands by different manufacturers, the technology is likely to be similar across brands and wherever possible similar diagnostic thresholds were selected for the analysis. However, although all the studies used microscopy as the reference standard, there was clear variation in both the microscopic methods used and the thresholds used to define the presence of haematuria. These varied between authors and even within studies: several authors tried out a range of different thresholds and derived different estimates of sensitivity and specificity for each dataset. Even where the explicitly stated thresholds were similar across studies, there is the potential for unobserved variation attributable to differential recording and interpretation of results between operators (for both dipsticks and microscopy). In addition, the time between dipstick and microscopic investigations was not always reported, although this factor is likely to have impacted on any subsequent estimates of diagnostic accuracy. Dipstick tests are usually conducted in a near-patient context, on fresh urine samples, and are largely designed to detect the presence of haemoglobin or the haem group. It may therefore be assumed that issues of sample stability are of limited relevance to the performance of these tests. By contrast, microscopic examination requires accurate counting of RBCs, which are unstable in urine samples. Delay between sample collection and microscopy, such as might commonly occur in the UK owing to transportation of samples to specialist laboratories for examination, is therefore likely to affect the validity of the reference standard. Although this is a factor of considerable interest, the review found no studies that quantified variation in the diagnostic performance of microscopy with time delay.

Once its presence has been established, the next logical step is to determine the underlying cause of haematuria. The studies identified in this review indicate that the simple detection of microhaematuria alone cannot be considered a useful diagnostic test for the presence of significant underlying pathology (urinary calculi or bladder cancer). Haematuria can occur as a result of numerous different underlying pathologies, and this is reflected in the wide variety of diagnostic tests applied to its investigation. One approach to rationalising the investigation process may be to optimise specialist

referral. Current UK clinical practice is to refer all patients with haematuria to urology, and then to nephrology as indicated. If a simple, non-invasive test were available which could identify, with acceptable accuracy, patients in whom a renal cause for haematuria is likely, then the overall burden of testing could be reduced. This would potentially lead to a decrease in cost and increase in acceptability to patients.

There are several tests that might direct referral for a patient with haematuria (e.g. proteinuria, serum creatinine, BP) that have not been fully evaluated in diagnostic accuracy studies in patients with haematuria. However, a large proportion of the included studies evaluated microscopy or automated methods to determine whether haematuria is renal or urological in origin through the examination of RBCs in the urine. These techniques are based on the notion that urinary erythrocytes of glomerular origin will appear dysmorphic on examination, or will differ in volume from cells originating in the lower urinary tract. In general, two approaches are taken when classifying the morphology of urinary blood cells: dual threshold and single threshold. Dual threshold studies each provided two cut-offs for the proportion of dysmorphic cells present in the urine; non-glomerular haematuria is diagnosed where the proportion of dysmorphic RBCs is less than the lower cut-off and glomerular haematuria where it is above the upper cut-off. If the urine contains a proportion of dysmorphic cells that lies between the cut-off values, a 'mixed' diagnosis is made. This 'mixed' diagnosis is essentially an uninformative result, so that, using this approach, any potential clinical and cost benefits accrued from correctly referring patients with clear glomerular or non-glomerular haematuria would need to be weighed against the potential increased cost and delay for patients who receive a 'mixed' diagnosis and require further testing. However, given that current UK practice is to refer all patients to urology for initial investigation, the alternative treatment of dichotomising data from dual threshold studies can be justified. This approach aims to identify patients who are highly likely to have a renal cause for haematuria and refer these directly to nephrology, thus avoiding unnecessary urological evaluations. Using this approach, patients with a 'mixed' or 'urological' result would be classified as test-negative and given a conventional referral to urology. Single threshold studies provide dichotomous data with no 'mixed' diagnoses. Hence, although the dichotomy of data may be clinically artificial, it has potential utility for rationalising referral. However, the cost of additional testing pre-referral, and also the delay involved for all patients, must be considered, given the relatively small numbers of patients who are likely to be identified as having haematuria of renal origin and referred directly to nephrology. Although the variation amongst the identified studies precluded any estimate of a 'best performance' threshold that could be applied across patient groups, studies of RBC morphology that used a cut-off value of 80% dysmorphic cells for glomerular disease reported consistently high specificities. It therefore seems likely that this threshold could be used to rule in a renal cause for haematuria and eliminate urological referral. Variation in the reported results makes it unclear what proportion of patients with a renal cause for haematuria would undergo urological referral if this cut-off were applied, although reported sensitivities were generally low. Current UK practice involves the use of general microscopy to screen for infection as a cause of haematuria and may also include a screen for red cell casts as an indicator of renal bleeding. Detailed examination of RBC morphological or volume characteristics is not common. Data from studies identified here were either too sparse or heterogeneous to establish any definite benefit from routine testing of this type. No difference in performance was indicated for PCM or laser microscopy over conventional light microscopy. As with quantification of urinary erythrocytes, accuracy of morphology is likely to be influenced by sample deterioration – something which was not investigated in the evidence identified for this report.

The majority of the remaining studies of tests used to investigate the cause of haematuria focused on diagnostic accuracy for the detection of lesions or tumours in patients with microscopic haematuria. Cystoscopy is generally considered to be the reference standard investigation for detecting lesions or tumours of the lower urinary tract. However, this is an invasive procedure (which can cause discomfort and carries a small risk of infection) and minimally invasive methods to identify tumours of the lower urinary tract, such as voided urinary markers and cytology, have been developed and evaluated. These methods also have potential use in identifying subgroups of patients with haematuria, with suspected tumours, who require confirmatory cystoscopy, that is, in reducing the number of patients requiring cystoscopy. A further potential use for minimally invasive testing lies in monitoring for recurrence of disease; this application lies outside the scope of the current review.

Most studies identified evaluated tumour markers that were explicitly intended to detect bladder cancer. There were only two markers that had been evaluated in more than one study: BTA and NMP22. There are numerous other tumour markers which have been developed (e.g. Lewis X Antigen, Telomerase, FDP, Cytokeratin 20, CD 44v), but the searches did not identify diagnostic accuracy studies of these markers in the population of interest defined for this project. The range of positive and negative LRs suggest that neither BTA nor NMP22 would be useful either for diagnosing bladder cancer or for ruling out patients for further investigation (cystoscopy). However, the evidence remains sparse and the diagnostic accuracy estimates varied widely between studies. Further investigation of the factors potentially responsible for this variation (e.g. patient characteristics, stage of disease) could indicate whether the markers can be made more accurate as a diagnostic test or more fruitfully applied in other contexts (e.g. monitoring for recurrence). However, given the findings of the current review, the AUA's statement that the available data are insufficient to recommend the routine use of voided urinary markers in patients with microscopic haematuria seems appropriate.

Like the tumour markers, cytology has been evaluated as a less invasive alternative to cystoscopy/biopsy in the diagnosis of urinary tract malignancies. As with the other groups of studies identified in this review, the studies evaluating cytology as a test for malignancy were heterogeneous, although there were more diagnostic accuracy data available for cytology than for the biochemical tumour markers. Sensitivity estimates for cytology varied dramatically from 3 to 100%. Although statistically heterogeneous, estimates of specificity were generally high (~90–100%), with only one clear outlier; cytology might therefore be useful in ruling in malignancy, but has no application in ruling out malignancy or excluding patients from further investigation (thereby possibly saving on the number of invasive tests that need to be conducted). We found no diagnostic accuracy studies that reported the differential accuracy of cytology in patients at high and low risk for bladder cancer.

Several different imaging modalities have been evaluated as tests to detect lesions or tumours. Imaging studies variously reported accuracy data for the detection of tumours, inflammatory lesions, calculi, structural abnormalities or combinations of some or all of these. With the exception of techniques such as virtual cystoscopy and DMSA scintigraphy, which target particular sections of the urinary tract, the remaining techniques were variously used to image the upper, lower or entire urinary tract. As a consequence, the pooling of imaging studies was precluded owing to the various aims of the investigations. Although certain imaging modalities might be more accurate for particular diagnostic aims, data from existing studies are insufficient to establish if this is the case. The most commonly evaluated techniques were IVU and ultrasound. However, even where both of these investigations were compared against a common reference standard of final diagnosis, the diagnostic aims and relative estimates of accuracy were inconsistent across studies. Several of the ultrasound investigations used IVU as the reference standard for imaging the kidneys and urinary tract. Although cystoscopy appears to be an acceptable reference standard for the detection of lesions/tumours of the bladder, there does not appear to be a clear reference standard for imaging the urinary tract as a whole. The use of IVU for this purpose may be questionable as, relative to final diagnosis, it has rarely been shown to be highly sensitive. The use of an imperfect reference standard can result in the misclassification of true- and-false positive and negative values, and therefore influence all subsequent diagnostic accuracy calculations. CT alone or in combination with other methods may have some potential as an imaging technique for detecting the cause of haematuria (and may have the additional benefit of imaging outside the urinary tract), but it is a reasonably new technology that has received little evaluation to date. Similarly, current ultrasound technology is likely to differ from that used in the ultrasound evaluation studies identified here, several of which were conducted 10–15 years ago.

In a clinical situation, such as investigation of the cause of established haematuria, where there are a number of potential target conditions and the reference standard of diagnosis is not defined, conventional diagnostic accuracy studies offer little insight into the effectiveness of testing. The consecutive, hierarchical nature of the diagnostic process proposed by Moons and Grobbee[1281] is of direct relevance to the question addressed by this review, namely, what is the most appropriate sequence of tests for the investigation of haematuria? Although each additional investigation conducted represents an increase in the burden of testing to the patient and an increase in costs, it is clear from the studies

included in this review that overlap in the information provided by different tests is likely. In order to address the primary research question for this project adequately it is necessary to quantify the extent to which each additional test or investigation cumulatively contributes to the diagnostic process. This can be achieved by using a multivariable prediction modelling approach to diagnostic study design[1282,1283] in place of traditional diagnostic accuracy comparisons.

Modelling methodology

It is acknowledged that the principal aim of modelling is to inform resource allocation decisions in the NHS and to seek an optimal solution in meeting this aim. These requirements have been recently discussed[1266] and argue for the following:

1. The specification of the decision problem should ideally include the comparison of all diagnostic strategies that could feasibly be used in the NHS. It is recognised, however, that, in practice, these options may be constrained by the availability of evidence and the structural complexity of any model.
2. The analysis should make a clear link between the diagnostic accuracy of a given strategy, the impact on therapy and the ultimate effect on health outcomes. Hence the effect of each of the four diagnosis groups – true positive, false negative, true negative and false positive – for the selection of therapies needs be assessed, along with the effect of such therapy on outcomes.
3. A lifetime time horizon is required for any economic evaluation in this area. This is because the sequelae of inappropriately managed patients in the investigation of haematuria, for some conditions, could affect the life expectancy and quality of life of patients.
4. The ultimate health effects of the alternative diagnostic strategies should be expressed in terms of a generic measure of health such as a quality-adjusted life-year (QALY). This is because it is necessary to assess the value of improved outcomes from more accurate diagnostic tests in units that can be compared with those of programmes and interventions in other specialties and disease areas, which are competing for finite healthcare resources.
5. The evidence that is used to establish the cost-effectiveness of the alternative diagnostic strategies needs to be identified systematically and synthesised appropriately.
6. The evidence used to estimate cost-effectiveness should be relevant to patients and clinical practice in the UK health service.
7. The uncertainty in the evidence base needs to be reflected in the model. To assess simultaneously the implications of uncertainty in all elements of evidence, probabilistic analysis should be used to establish the decision uncertainty associated with each diagnostic strategy being compared.[1284–1286] This informs decision-makers about the probability of each strategy being the most cost-effective conditional on the value the decision-maker places on a unit of health gain. Such methods can be used to provide an opportunity to use value of information methods to inform priority setting in research.[1287,1288]

In the modelling solutions provided in the present study, the aim has been to take into account the complexity and challenges that are faced by the modelling of algorithms for the detection of microscopic haematuria and its underlying causes. This complexity perhaps explains the lack of decision analytic studies in the literature comprehensively investigating haematuria algorithms, whether short-term or otherwise.

Cost data used in the modelling were derived from NHS reference costs, PSSRU data or an NHS Trust hospital. This ensures that the models appropriately reflect the perspective of the UK NHS.

In terms of point (1) above, the modelling solutions, although constrained by some gaps in the evidence base, have provided clinicians and decision-makers with a clear picture of where variation exists throughout the diagnostic algorithm and the relative efficiency of alternative technologies that can be applied at these points. By producing separate models for areas of variation, the solutions should facilitate an understanding of the trade-offs that can be made in terms of cases detected, numbers of false results and the relative cost-effectiveness of strategies. Owing to the heterogeneity in outcome of interest and the large numbers of alternative strategies and embedded decision nodes, it was not feasible to model a large series of unique strategies, although there is clearly merit in striving to achieve such a solution.

It is acknowledged that owing to the input in time and resources required to provide the current

modelling solutions, it has not been feasible to explore the impact of long-term health outcomes of alternative diagnostic strategies. In terms of point (2) above, the present solutions do provide a valuable platform to undertake long-term modelling in order to inform resourcing decisions better in the NHS. In this regard, the emphasis should be placed on the early detection of haematuria at initial testing in high-risk groups (especially for bladder cancer) and the impact of early versus late detection of tumours in the imaging and lower urinary tract models (through the use of screening and follow-up investigations with more accurate or reference standard tests). If patients with a negative finding after undergoing a full evaluation for underlying causes of haematuria (irrespective of its form and relative efficiency) are followed up through regular screening, any time delay between 'early' and 'late' detection is likely to be relatively short. In contrast, if patients with haematuria are missed through a low-accuracy 'incidental' assessment and fail to have a timely evaluation, their condition will not be detected until after they become symptomatic and may have progressed to a later stage with poorer prognoses[1268] and higher costs.[1049]

As the outcome of effect was cases detected, a short-term horizon was adopted in the present study. Once long-term health outcomes are considered, as advocated in point (3) above, for an underlying cause of microscopic haematuria of interest, a lifetime horizon should be utilised.

As an intermediate outcome of cases detected was used in the present study, it will not be possible to compare the results with other programmes through the use of generic measures such as QALYs, as outlined in point (4).

The modelling has met the criterion of point (5) above in that all diagnostic accuracy data were derived from the systematic review.

The recommendation for using probabilistic sensitivity analysis, point (7), has been met by the modelling solutions presented in this report, which provide decision-makers and clinicians with a good overview of how uncertainty in the data may impact on the cost-effectiveness results. Although formal expected value of perfect information analyses have not been undertaken, the models have appropriately identified areas that would benefit from further research and improved data quality (especially in the use of routine microscopy in the primary care setting).

Results of review of economics studies

Eight studies met the inclusion criteria for the review and were data extracted and assessed for quality using both the NHS EED template and a conventional checklist. The underlying finding in terms of the direction of costs and effects was assessed using the hierarchical decision matrix.

The principal findings from these studies [see the sections 'Summary of included studies' (p. 77) and 'Summary of included abstracts' (p. 82)] can be summarised as follows:

- Cytology, consistent with AUA guidelines, should be conducted only on high-risk patients for transitional cell carcinoma.
- Asymptomatic haematuria, whether gross or microscopic, is a significant finding and warrants evaluation from a risk–benefit and cost-effectiveness standpoint.
- Patients with intermediate urine cytology results, who are non-smokers and have neither haematuria nor a history of urothelial cancer, are at low risk of malignancy and do not warrant complete evaluation.
- A neural network of three tumour markers can avoid invasive cystoscopy and be cost saving in comparison with haematuria/cytology in patients being screened for bladder cancer.
- Complete urological work-up for asymptomatic microhaematuria should be restricted to patients with normocytic or mixed haematuria, as identified by RDCs.
- The use of tumour markers (NMP22) can result in cost savings and avoid cystoscopy in patients being investigated for bladder cancer.
- Screening males over 50 years of age for haematuria with dipsticks results in an acceptable incremental cost per LY gained in comparison with other screening programmes.

These studies addressed different parts of the diagnostic chain but no single study addressed the complete diagnostic process. The review also highlighted a number of methodological limitations in these studies.

Separate decision analytic models were therefore developed to progress estimation of the optimal strategy for the diagnostic management of haematuria.

Results of economic modelling

Detection of microscopic haematuria

The decision tree represents UK clinical practice in presenting all plausible strategies that can be adopted in the detection of microscopic haematuria. Immediate microscopy, conducted under ideal conditions, can be regarded as the reference standard and for all prevalence values correctly identifies all cases, thus eliminating additional unnecessary costs associated with false positives and repeat testing associated with false negatives. Routine microscopy is associated with a reduction in test accuracy – principally sensitivity (estimated by the review panel owing to the lack of data from the literature). Strategies using routine microscopy were found to produce large numbers of false-negative results, of most concern for potential losses in health and quality of life. Dipstick testing was associated with high numbers of false-positive results. These could be eliminated if immediate microscopy were used to confirm positive results. Routine microscopy, as a confirmation test for a positive dipstick result, generates further false results.

In order to acquire the additional benefits of immediate microscopy (over the next best alternative of dipstick testing or dipstick followed by immediate microscopy), decision-makers would need to be willing to pay an additional £2000 for a probability of 0.7 of this being cost-effective for high-risk patients (prevalence 10%). This value increases for lower prevalence values and could be as high as £5000 in testing young adults. It should be noted that the cost estimates for the setting up of facilities to undertake immediate microscopy were not considered, and the model assumed that these were available within the NHS. If policy makers were to provide facilities to use immediate microscopy routinely there would be additional budgetary implications for the NHS.

The modelling of this part of the algorithm strongly indicates the need for further research into the test accuracy of routine microscopy. Under best estimates, the results indicate that as a confirmation test for dipstick-positive results this method may well be associated with adverse economic and health consequences.

Imaging of the upper urinary tract to investigate the underlying cause of haematuria

In the 'any cause' model, CT and US were found to be the two principal choices, with CT being much more expensive, able to detect all cases and producing a very low number of false-positive results. US, based on the data used, is a low-cost and effective option and consideration should be given to its use as the first choice strategy for imaging of the upper urinary tract. This needs to be evaluated in further research as the present results are based on a single study. Decision-makers would need to be willing to pay very high amounts to acquire the additional cases detected by CT, suggesting that CT should only be used in limited scenarios. When either CT or IVU is used as a follow-up test after screening reveals persistent haematuria, all strategies ending with CT detect all cases. Only the US followed by IVU strategy fails to detect all cases. To assess fully the consequences of accepting the economic advantages of using US followed by CT, the impact on health outcomes such as survival and quality of life would need to be assessed for underlying causes of haematuria that may progress in the time delay between initial imaging and delayed imaging with CT. US, in combination with KUB X-ray, may be even more cost-effective than demonstrated in the present modelling. Data were not available to assess US and KUB.
In the case of tumour detection, only two strategies were evaluated (US and IVU). The results suggest that US is both more effective and much less costly than IVU. However, the uncertainty in the data does not permit a strong conclusion as the sensitivity analysis revealed that IVU can be more effective than US in some scenarios.

Investigation of the lower urinary tract to determine the underlying cause of microscopic haematuria

The strategies examined were considered relevant for present and potential future clinical practice (virtual cystoscopy and cystosonography are not currently used in the UK). Available tumour markers from the systematic review, along with cytology, virtual cystoscopy and cystosonography, were considered as initial tests prior to cystoscopy for those with a positive result. The model only considered low-risk patients, as high-risk patients receive immediate cystoscopy in the standard algorithm for the UK. Currently, it is common also to carry out immediate cystoscopy (the gold standard) on low-risk patients and therefore the aim of the model was to evaluate the trade-offs in costs and effect at both initial investigation, and for those with persistent haematuria on follow-up screening with (delayed) cystoscopy.

Cytology followed by cystoscopy (for positive cytology results) was found to detect the least

number of cases at initial investigation. The most effective tumour marker was found to be MCM5. However, all strategies (except cystoscopy alone) miss some cases. The incremental cost-effectiveness of moving from MCM5 to cystoscopy alone for all patients was £49,000. When screening negative patients with follow-up cystoscopy was added, all strategies detected all cases in the original cohort, with 'cytology followed by cystoscopy' as the initial investigation producing the lowest cost. However, the sensitivity analysis revealed that the strategy that commenced with MCM5 cystoscopy could also be the least costly strategy.

Moving to strategies that did not commence with immediate cystoscopy would be associated with economic benefits, but there is a risk that patients with serious and life-threatening conditions (principally TCC) would be missed at initial investigation, resulting in worse long-term health outcomes and increased costs, which may offset the initial gains. The impact on long-term health outcomes and costs for early versus late tumour detection should be evaluated before a different algorithm for high- and low-risk patients can be recommended.

Chapter 9
Conclusions

The primary objective of this project was to determine the most effective and cost-effective diagnostic strategy for the investigation of haematuria. Although many diagnostic algorithms have been published, the review identified none that had been rigorously evaluated. The potential causes of haematuria are numerous and clinical practice in the UK currently uses a wide variety of tests in its investigation. Similarly, a number of alternative tests, which are not widely used in clinical practice, have been evaluated in research settings. This is reflected in the high degree of heterogeneity in the studies identified by this review. Studies varied greatly, both in clinical objective (target condition) and in tests evaluated for similar target conditions. The derivation of firm conclusions is further inhibited by the poor methodological and reporting quality of the studies included in the review.

Given the paucity of evidence, deficiencies in primary study quality and large number of important research questions that remain to be addressed, it is not possible to derive an algorithm of the diagnostic pathway for haematuria that would be solely supported by existing evidence. A hypothetical algorithm based on the opinion and practice of clinical experts on the review team, together with the evidence identified through the review process, is presented in Appendix 12. This algorithm is presented, for comparative purposes, alongside existing USA (AUA) and UK (SIGN) guidelines and is not intended as a guide for current practice. It is hoped that the information contained in these algorithms, alongside the questions outlined in the section 'Implications for research' (p. 121), will inform future primary and secondary research.

Determining the presence of microhaematuria

The evidence from the majority of studies included in the review suggests that dipstick testing may provide a moderately useful indicator of the presence of haematuria (i.e. a positive dipstick test is reasonably likely to represent the presence of haematuria), which can be used in a general practice setting. The sensitivities calculated for included studies were generally poor, precluding the use of dipstick testing to rule out haematuria. The included studies showed considerable clinical and statistical heterogeneity. Any conclusions regarding the immediate utility of dipstick testing should therefore be considered with extreme caution. The context in which the dipstick test is to be used warrants particular consideration. The studies identified in this review indicate that the simple detection of microhaematuria cannot be considered a useful diagnostic test for the presence of significant underlying pathology (urinary calculi or bladder cancer). With this in mind, the potential use of dipsticks to rule in haematuria is of limited clinical value. Similarly, the absence of haematuria on a single dipstick test cannot reasonably be used to rule out symptomatic patients from further investigation. However, no data were identified on the relationship between repeat positive tests and the presence of disease. The usefulness of dipstick testing in this context therefore remains open to question. There is no trial-based evidence regarding the effectiveness of screening for haematuria in the general population to identify life-threatening pathologies (e.g. bladder cancer).

The confirmation of haematuria using microscopy under ideal conditions (i.e. taking measures to eliminate sample degradation) remains a valid option where further investigations are being considered. As stored samples are theoretically subject to degradation and the effect of this degradation on the diagnostic performance of microscopy has not been quantified, the practice of sending a urine sample taken in the community for laboratory confirmation of haematuria appears to be of questionable value. Such samples may still, however, be useful to eliminate UTI as a cause of haematuria.

Investigating the cause of haematuria

No data were identified on the clinical effectiveness of investigations to determine the cause of haematuria. It therefore remains open to question whether and at what point patients with haematuria should be actively investigated. If further

investigation of patients with haematuria is contemplated, it would be desirable to reduce the number of investigations required by optimising referral. Microscopic methods for localising the source of bleeding have been widely evaluated and may have the potential to aid in directing referral. However, there are currently organisational, technological and knowledge barriers which prevent the recommendation of the routine use of these techniques to direct referral from primary care.

The focus of much investigation of haematuria is the identification of life-threatening malignancies of the lower urinary tract. The reference standard of diagnosis is cystoscopy and, as such, less-invasive methods of identifying malignancy or focusing further testing are desirable. Considerable attention has been given, in recent years, to the development of biochemical tumour markers measurable in the urine or plasma of patients. Diagnostic accuracy studies included in this review indicated that the tumour markers evaluated would be useful neither for ruling in nor ruling out malignancy. However, a number of other tumour markers exist (e.g. Lewis X Antigen, Telomerase, FDP, Cytokeratin 20, CD 44v) for which no evaluation of diagnostic accuracy was identified. The diagnostic performance of these remains unknown. In addition, it is possible that combinations of markers or sequential testing in individual patients may have greater diagnostic value; no data were identified on these applications. Urine cytology represents a more established 'screening' test for urological malignancy. As with other areas of the review, diagnostic accuracy studies of urine cytology were heterogeneous and poorly reported. The calculated specificity values were generally high, suggesting some possible utility in confirming malignancy. However, the evidence suggests that urine cytology has no application in ruling out malignancy or excluding patients from further invasive investigations.

A number of different imaging modalities have been evaluated as tests to detect different or general underlying causes of haematuria. There is overlap between conditions targeted by the different imaging modalities. The evidence from studies included in the review was insufficient to draw any firm conclusions regarding the diagnostic accuracy of imaging studies in determining the cause of haematuria. Economic evaluations suggest that ultrasound followed by CT for patients with a negative test, but found to have persistent haematuria during follow-up screening, may be a cost-effective approach. In the absence of firm supporting evidence, the decision on whether or not to conduct imaging investigations should be made on an individual patient basis. Research into the cumulative diagnostic value of imaging investigations as well as their effects on long-term patient outcome is urgently required.

Implications for clinical practitioners and decision-makers

- The evidence identified in the systematic review does not support a diagnostic link between a single test for haematuria and presence of significant pathology and there is an absence of evidence on the effectiveness of screening for haematuria in either general or targeted populations. Practitioners should consider carefully before testing for haematuria.
- The systematic review provided no evidence on the utility of testing for recurrent haematuria as a guide for further investigation. In the light of the evidence against the value of single testing for haematuria, and giving consideration to current expert opinion, practitioners may wish to consider confirming persistent haematuria by repeat testing before referring for further investigation.
- Practitioners might consider further laboratory testing (immediate microscopy), in cases of confirmed haematuria, in order to direct referral.
- Evidence identified by the systematic review suggested that neither tumour markers nor urine cytology can currently be used alone to rule out malignancy or to rule out patients from further investigation. The results of the modelling suggest that, if a sufficiently accurate tumour marker were available (e.g. MCM5), initial testing with follow-up screening using cystoscopy for patients with persistent haematuria would be associated with economic savings and eventually detect all tumours. The lack of data regarding the impact of delayed detection on health outcomes and costs in the long term should be considered before this approach is adopted in UK practice.
- The findings of the modelling suggest that US as an initial imaging test, followed by CT for those with a negative test and persistent haematuria at follow-up, may be a cost-effective approach. However, clinicians may require stronger evidence to make confident decisions on whether or not to conduct such imaging studies.
- Further research is urgently required on the effectiveness (in terms of patient outcome) of testing for and investigating the cause of haematuria in order to inform policy in these areas.

Implications for research

Quality assessment highlighted the poor methodological and reporting quality of many studies included in this review. Future evaluations of diagnostic tests should follow the STARD guidelines for reporting of diagnostic accuracy studies.[1277,1278] Specific questions requiring further research are:

- Is screening/testing for haematuria effective? Large, well designed and appropriately powered RCTs of screening versus no screening are required in target populations and/or the general population. These should measure patient outcomes in terms of morbidity and mortality relating to appropriate target conditions (probably urological malignancy).
- Is investigation of the cause of haematuria effective? Research in this area is urgently required. The ideal approach would use an RCT design to compare alternative testing strategies in terms of patient outcome (probably urological malignancy). The effectiveness of investigation in differing patient populations (e.g. an incidental finding of haematuria versus haematuria in a symptomatic patient) should also be considered. An alternative approach would involve a combination of studies of accuracy of testing and intervention trials to demonstrate improved outcomes resulting from earlier diagnosis.
- What is the most effective means of following those with haematuria who test negative on all initial investigations? Specifically, what repeat screening test should be done, at what frequency and for how long, and what are the indications for repeat or additional investigations? Large, well designed and appropriately powered RCTs comparing different follow-up strategies in target populations are a possibility. Alternatively, a multi-variable prediction modelling approach could be used to assess the effects of variation in repeat testing, time interval and duration of follow-up.
- Although one study confirmed the notion that macrohaematuria is a highly specific indicator of bladder cancer, there is a distinct lack of good quality evidence on macrohaematuria. Are there subgroups of patients with macrohaematuria (other than young women with established UTI) for whom investigation is not mandatory? What is an appropriate approach to follow-up in macrohaematuric patients after negative investigation?
- Can dipstick tests be used to detect haematuria? Existing studies are statistically and clinically heterogeneous. Further well-conducted diagnostic accuracy studies in this area may be useful. Future studies should define and employ a standard method and threshold for the reference standard (microscopy).
- What is the impact of sample degradation with time on the performance of microscopy for the detection of haematuria? Comparative diagnostic accuracy studies (microscopy on routine samples taken in the community and transported to the laboratory versus immediate microscopy) are required in order to quantify this effect.
- What would be the incremental benefit of routinely using urinary blood cell morphology techniques alongside simple renal function tests (e.g. proteinuria) in order to improve direct referral to nephrology?
- What are the factors affecting the performance of urine cytology? The reported diagnostic performance of urine cytology is extremely variable. Future studies to investigate sources of variation (e.g. operator skill) with the aim of refining methods to improve accuracy and consistency may therefore be useful.
- What are the clinical applications of biochemical tumour markers? Well conducted and reported diagnostic accuracy studies are required to quantify the performance of those tumour markers not yet evaluated. In addition, studies addressing the accuracy effects on diagnostic performance of using tumour markers in combination or in serial measurements in the individual patient are required.
- What is the cumulative diagnostic effect of additional imaging studies? The cumulative sequential nature of the investigation process can best be evaluated using a multi-variable prediction modelling approach to diagnostic study design, as described in the discussion section.
- What are the clinical and economic impacts on delayed detection for upper tract tumours through the introduction of US as an initial imaging test, if CT is used as a follow-up test for screened patients with persistent haematuria?
- What are the clinical and economic impacts on delayed detection for lower tract tumours through the use of tumour markers (and cytology) as an initial investigation, if cystoscopy is used as a follow-up test for screened patients with persistent haematuria?

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Contribution of authors

Mark Rodgers (Research Fellow) prepared the protocol design and carried out the collection, analysis and interpretation of data, and contributed to writing and editing the report. John Nixon (Research Fellow, Health Economics) prepared the economics section of the protocol, reviewed the algorithms and was responsible for the economics sections of the report. Susanne Hempel (Research Fellow) worked on inclusion screening, analysis and interpretation, and contributed to writing and editing the report. Tevita Aho (Consultant Neurologist) worked on inclusion screening, algorithm review and construction, interpretation of data, and contributed to editing the report. John Kelly (Consultant Neurologist) and David Neal (Professor of Surgical Oncology) provided clinical input/advice for the project in addition to reading and providing comments on the draft protocol and all versions of the report. John Kelly also attended project meetings in York and assisted in identifying relevant contributions from recent conference proceedings. Steven Duffy (Information Officer) managed and checked references and was responsible for the search strategy and running update searches. Gill Ritchie (Information Scientist) developed search strategies, carried out searches and managed the bibliographic database. Jos Kleijnen (Institute Director, Centre for Reviews and Dissemination) contributed to protocol design, inclusion screening and gave guidance on the collection, analysis and writing of the report. Marie Westwood (Senior Research Fellow) wrote the proposal protocol and carried out collection analysis and interpretation of data, and gave guidance on writing and editing the report.

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Appendix 1

Advisory panel members

Dr John Bradley
Clinical Director of Renal Services, Dialysis Centre, Addenbrooke's Hospital, Cambridge

Professor Ian Watt
Professor of Primary and Community Care, University of York

Professor Mark Sculpher
Professor of Health Economics, Centre for Health Economics, University of York

Professor Adrian Dixon
Clinical Director of Radiology, University of Cambridge, Department of Radiology, Addenbrooke's Hospital, Cambridge

Patient of Professor Adrian Dixon

Appendix 2

Detailed search strategies

A wide range of databases and other information resources were searched to locate details of both published and unpublished studies and other information on the clinical effectiveness and cost-effectiveness of diagnostic tests for the investigation of haematuria.

The draft strategy used to carry out the scoping review was further developed following consultation with clinical experts and from the papers found during the scoping exercise. This strategy was then adapted to run on the other databases selected to search. All initial searches were carried out between October and December 2003. All resources were searched from their inception to the most recent date available. There was no restriction on study by country of origin, language or publication date. The bibliographies of retrieved references were checked for additional publications. The results of the searches were imported into Endnote5 bibliographic management software and deduplicated.

The following medical databases were searched: MEDLINE, EMBASE, BIOSIS, Pascal, Science Citation Index and LILACS.

The following unpublished or grey literature sources were searched: *ISI Proceedings*, *Dissertation Abstracts*, Systems for Information in Grey Literature (SIGLE), MetaRegister of Current Controlled Trials (mRCT), National Research Register (NRR), NTIS (National Technical Information Service) and GrayLit Network.

The following Internet sites were searched: OMNI (Organising Medical Networked Information) and Google.

The following economic sources were searched: NHS EED (NHS Economic Evaluations Database), OHE HEED (Office of Health Economics Health Economics Evaluations Database) and Economics Working Paper Archive. Additional searches were carried out on MEDLINE and EMBASE for the economic modelling and are listed at the end of this Appendix.

Update searches were completed on 29 July 2004. The results of the update searches are listed on p.180.

MEDLINE 1966–2003/October week 3. Accessed via Ovid web (http://gateway1.uk.ovid.com/ovidweb.cgi)
Searched 28 October 2003. Retrieved 6683 records.

1. Hematuria/
2. (hematuria or haematuria).ti,ab.
3. (microhematuria or microhaematuria).ti,ab.
4. (macrohematuria or macrohaematuria).ti,ab.
5. ((blood cell$ or red cell$ or occult blood) adj2 urin$).ti,ab.
6. or/1-5
7. exp Diagnostic Techniques, Urological/
8. Radiography/
9. exp Radiography, Abdominal/
10. Ultrasonography/
11. Endosonography/
12. exp Ultrasonography, Doppler/
13. Ultrasonography, Interventional/
14. exp Tomography, Emission-Computed/
15. Tomography, X-Ray Computed/
16. exp Magnetic Resonance Imaging/
17. exp Reagent Kits, Diagnostic/
18. flow cytometry/ or image cytometry/
19. exp Biological markers/
20. exp Microscopy/
21. (urinalys$ or urograph$ or ivu or pyelograph$ or pyelogram$ or ivp or ureteroscop$ or cystoscop$).ti,ab.
22. ((renal or kidney) adj2 biops$).ti,ab
23. (urin$ adj2 (culture$ or densit$ or sediment$ or cytolog$ or cytopath$ or microscop$)).ti,ab.
24. (dipstick$ or dip stick$ or reagent strip$ or test strip$ or sediment$ count$).ti,ab.
25. (xray$ or x ray$ or ultrasound or ultrasonograph$ or endosonograph$ or endoscop$).ti,ab.
26. (tomograph$ or cat scan$ or pet scan$ or ct).ti,ab.
27. (imaging or mri or radiologic$ or radiograph$).ti,ab.
28. (flowcytomet$ or flow cytomet$ or flowmetry or image cytomet$).ti,ab.
29. ((tumor$ or tumour$ or biologic$) adj marker$).ti,ab.
30. (diagnostic algorithm$ or diagnostic procedure$ or diagnostic rule$ or diagnostic tool$).ti,ab.
31. or/7-30

32. 6 and 31
33. exp "sensitivity and specificity"/
34. predictive value of tests/
35. false positive reactions/
36. false negative reactions/
37. logistic models/
38. ROC curve/
39. likelihood functions/
40. exp diagnostic errrors/
41. Diagnosis, Differential/
42. (diagnos$ adj3 (efficen$ or efficac$ or effectiv$ or accura$ or correct$ or reliable or reliability or error$ or mistake$ or inaccura$ or incorrect or unreliable)).ti,ab.
43. (reference test or reference tests or reference testing).ti,ab.
44. (sensitivity adj3 (test or tests)).ti,ab.
45. (specificity adj3 (test or tests)).ti,ab.
46. (predictive standard$ or predictive value$ or predictive model$ or predictive factor$).ti,ab.
47. (sroc or srocs or roc or rocs).ti,ab.
48. (receiver operat$ curve$ or receiver operat$ character$).ti,ab.
49. likelihood ratio$.ti,ab.
50 (false positive$ or false negative$).ti,ab.
51. (true negative$ or true positive$).ti,ab.
52. (positive rate$ or negative rate$).ti,ab.
53. (accura$ adj2 (test or tests or testing or standard$ or score$ or aid or aids)).ti,ab.
54. (reliable adj2 (test or tests or testing or standard$)).ti,ab.
55. (reliability adj2 (test or tests or testing or standard$)).ti,ab.
56. (performance adj2 (test or tests or testing or standard$)).ti,ab.
57. misdiagnos$.ti,ab.
58. or/33-57
59. 58 and 6
60. 32 or 59
61. animal/
62. human/
63. 61 not (61 and 62)
64. 60 not 63

EMBASE 1980–2003/week 42. Accessed via Ovid web (http://gateway2.uk.ovid.com/ovidweb.cgi) Searched 28 October 2003. Retrieved 5626 records.

1. Hematuria/
2. (hematuria or haematuria).ti,ab.
3. (microhematuria or microhaematuria).ti,ab.
4. (macrohematuria or macrohaematuria).ti,ab.
5. ((blood cell$ or red cell$ or occult blood or rbc) adj2 urin$).ti,ab.
6. or/1-5
7. exp Urologic Examination/
8. exp bladder examination/
9. exp kidney examination/
10. Radiography/
11. Abdominal Radiography/
12. exp urinalysis/
13. exp urography/
14. exp pyelography/
15. exp computer assisted Tomography/
16. exp radiodiagnosis/
17. exp Reagent Kits, Diagnostic/
18. flow cytometry/
19. image cytometry/
20. ureteroscopy/
21. urethroscopy/
22. kidney biopsy/
23. Biological marker/
24. cell marker/
25. tumor marker/
26. exp reagent/
27. Test strip/
28. urine sediment/
29. exp Microscopy/
30. diagnostic procedure/
31. (urinalys$ or urograph$ or ivu or pyelograph$ or pyelogram$ or ivp or ureteroscop$ or cystoscop$ or cystography).ti,ab.
32. ((renal or kidney) adj2 biops$).ti,ab.
33. (urin$ adj2 (culture$ or densit$ or sediment$ or cytolog$ or cytopath$ or microscop$)).ti,ab.
34. (dipstick$ or dip stick$ or reagent strip$ or test strip$ or sediment$ count$).ti,ab.
35. (xray$ or x ray$ or ultrasound or ultrasonograph$ or endosonograph$ or endoscop$).ti,ab.
36. (tomograph$ or cat scan$ or pet scan$ or ct).ti,ab.
37. (imaging or mri or radiologic$ or radiograph$).ti,ab.
38. (flowcytomet$ or flow cytomet$ or flowmetry or image cytomet$).ti,ab.
39. ((tumor$ or tumour$ or biologic$) adj marker$).ti,ab.
40. (diagnostic algorithm$ or diagnostic procedure$ or diagnostic rule$ or diagnostic tool$).ti,ab.
41. or/7-40
42. 6 and 41
43. "sensitivity and specificity"/
44. Laboratory Diagnosis/
45. receiver operating characteristic/
46. logistic regression analysis/
47. ROC curve/
48. likelihood functions/
49. diagnostic error/
50. Differential Diagnosis/
51. (diagnos$ adj3 (efficien$ or efficac$ or effectiv$ or accura$ or correct$ or reliable or

reliability or error$ or mistake$ or inaccura$ or incorrect or unreliable)).ti,ab.
52. (reference test or reference tests or reference testing).ti,ab.
53. (sensitivity adj3 (test or tests)).ti,ab.
54. (specificity adj3 (test or tests)).ti,ab.
55. (predictive standard$ or predictive value$ or predictive model$ or predictive factor$).ti,ab.
56. (sroc or srocs or roc or rocs).ti,ab.
57. (receiver operat$ curve$ or receiver operat$ character$).ti,ab.
58. likelihood ratio$.ti,ab.
59. (false positive$ or false negative$).ti,ab.
60. (true negative$ or true positive$).ti,ab.
61. (positive rate$ or negative rate$).ti,ab.
62. (accura$ adj2 (test or tests or testing or standard$ or score$ or aid or aids)).ti,ab.
63. (reliable adj2 (test or tests or testing or standard$)).ti,ab.
64. (reliability adj2 (test or tests or testing or standard$)).ti,ab.
65. (performance adj2 (test or tests or testing or standard$)).ti,ab.
66. misdiagnos$.ti,ab.
67. or/43-66
68. 6 and 67
69. 42 or 68
70. exp animal/
71. exp nonhuman/
72. 70 or 71
73. exp human/
74. 72 not (72 and 73)
75. 69 not 74

BIOSIS 1969–2003/October week 3. Accessed via Dialog (file 5)
Searched 29 October 2003. Retrieved 1782 records.

1. S (hematuria or haematuria)/ti,de
2. S (microhematuria or microhaematuria)/ti,de
3. S (macrohematuria or macrohaematuria)/ti,de
4. S ((blood(W)cell or blood(W)cells or red(W)cell or red(W)cells or occult(W)blood or rbc) (2W) (urine or urinary))/ti,de
5. S s1 or s2 or s2 or s4
6. S (urinalysis or urography or urographic or ivu or pyelography or pyelogram or pyelograms or ivp)/ti,de
7. S (ureteroscop? or cystoscop? or cystography)/ti,de
8. S (renal(2W)biopsy or renal(2W)biopsies or kidney(2W)biopsy or kidney(2W)biopsies)/ti,de
9. S ((urine or urinary) (2W) (culture or cultures or density or densities or sediment or sediments))/ti,de
10. S ((urine or urinary) (2W) (cytology or cytologies or cytopathology or cytopathologies or microscopy or microscopic or microscope))/ti,de
11. S (dipstick? or dip(W)stick? or reagent(W)strip or reagent(W)strips or test(W)strip or test(W)strips or sediment?(W)count or sediment?(W)counts)/ti,ab
12. S (xray or xrays or x(W)ray or x(W)rays or ultrasound)/ti,de
13. S (ultrasonography or endosonography or endoscopy or endoscopic or endoscopies)/ti,de
14. S (tomography or tomographies or pet(W)scan or pet(W)scans or pet(W)scanning)/ti,de
15. S (cat(W)scan or cat(W)scans or cat(W)scanning or ct(W)scan or ct(W)scans or ct(W)scanning)/ti,de
16. S (magnetic(W)resonance(W)imaging or mri or nmr(W)imaging or mr(W)imaging or chemical(W)shift(W)imaging)/ti,de
17. S (radiologic or radiological or radiologically or radiograph or radiography)/ti,de
18. S (flowcytometry or flow(W)cytometry or flowmetry or image(W)cytometry)/ti,de
19. S ((tumor or tumors or tumour or tumours or biologic or biological)(W)(marker or markers))/ti,de
20. S (diagnostic (W) (algorithm? or procedure? or rule or rules or tool or tools))/ti,de
21. S ((diagnosis or diagnostic or diagnostically) (3N) (efficient or efficiently or efficiency))/ti,de
22. S ((diagnosis or diagnostic or diagnostically) (3N) (efficacy or efficacies))/ti,de
23. S ((diagnosis or diagnostic or diagnostically) (3N) (accuracy or accurately or accurate))/ti,de
24. S ((diagnosis or diagnostic or diagnostically) (3N) (correct or corrects or correctly or corrected))/ti,de
25. S ((diagnosis or diagnostic or diagnostically) (3N) (reliable or reliability))/ti,de
26. S ((diagnosis or diagnostic or diagnostically) (3N) (error or errors))/ti,de
27. S ((diagnosis or diagnostic or diagnostically) (3N) (mistake or mistakes or mistaken or mistook))/ti,de
28. S ((diagnosis or diagnostic or diagnostically) (3N) (inaccurate or inaccurately or inaccuracy or inaccuracies))/ti,de
29. S ((diagnosis or diagnostic or diagnostically) (3N) (incorrect or incorrectly))/ti,de
30. S ((diagnosis or diagnostic or diagnostically) (3N) (unreliable or unreliability))/ti,de
31. S (reference (W) (test or tests or testing))/ti,de
32. S (sensitivity (3N) (test or tests))/ti,de
33. S (specificity (3N) (test or tests))/ti,de

34. S (predictive (w) (standard or standards or value or values or model or models or factor or factors))/ti,de
35. S (sroc or srocs or roc or rocs)/ti,de
36. S (receiver(W)operat?(W)curve or receiver(W)operat?(W)curves)/ti,de
37. S (receiver(W)operat?(W)Character or receiver(W)operat?(W)characteristic?)/ti,de
38. S (likelihood(W)ratio or likelihood(W)ratios)/ti,de
39. S (false(W)positive or false(W)positives or false(W)negative or false(W)negatives)/ti,de
40. S (true(W)negative or true(W)negatives or true(W)positive or true(W)positives)/ti,de
41. S (positive(W)rate or positive(W)rates or negative(W)rate or negative(W)rates)/ti,de
42. S ((accurate or accuracy or accuracies) (2N) (test or tests or testing))/ti,de
43. S ((accurate or accuracy or accuracies) (2N) (standard or standards))/ti,de
44. S ((accurate or accuracy or accuracies) (2N) (score or scores))/ti,de
45. S ((accurate or accuracy or accuracies) (2N) (aid or aids))/ti,de
46. S (reliable (2N) (test or tests or testing))/ti,de
47. S (reliable (2N) (standard or standards))/ti,de
48. S (reliability (2N) (test or tests or testing))/ti,de
49. S (reliability (2N) (standard or standards))/ti,de
50. S (performance (2N) (test or tests or testing))/ti,de
51. S (performance (2N) (standard or standards))/ti,de
52. S (misdiagnosis or misdiagnostic or misdiagnose)/ti,de
53. S s6 or s7 or s8 or s9 or s10 or s11 or s12 or s13 or s14 or s15 or s16 or s17 or s18 or s19 or s20 or s21 or s22 or s23 or s24 or s25 or s26 or s27 or s28 or s29 or s30 or s31 or s32 or s33 or s34 or s35 or s36 or s37 or s38 or s39 or s40
54. s s41 or s42 or s43 or s44 or s45 or s46 or s47 or s48 or s49 or s50 or s51 or s52
55. s s53 or s54
56. S s5 and s55

Pascal 1973–2003/October week 3. Accessed via Dialog (file 144)
Searched 29 October 2003. Retrieved 623 records.

1. S (hematuria or haematuria)/ti,de
2. S (microhematuria or microhaematuria)/ti,de
3. S (macrohematuria or macrohaematuria)/ti,de
4. S ((blood(W)cell or blood(W)cells or red(W)cell or red(W)cells or occult(W)blood or rbc) (2W) (urine or urinary))/ti,de
5. S s1 or s2 or s2 or s4
6. S (urinalysis or urography or urographic or ivu or pyelography or pyelogram or pyelograms or ivp)/ti,de
7. S (ureteroscop? or cystoscop? or cystography)/ti,de
8. S (renal(2W)biopsy or renal(2W)biopsies or kidney(2W)biopsy or kidney(2W)biopsies)/ti,de
9. S ((urine or urinary) (2W) (culture or cultures or density or densities or sediment or sediments))/ti,de
10. S ((urine or urinary) (2W) (cytology or cytologies or cytopathology or cytopathologies or microscopy or microscopic or microscope))/ti,de
11. S (dipstick? or dip(W)stick? or reagent(W)strip or reagent(W)strips or test(W)strip or test(W)strips or sediment?(W)count or sediment?(W)counts)/ti,ab
12. S (xray or xrays or x(W)ray or x(W)rays or ultrasound)/ti,de
13. S (ultrasonography or endosonography or endoscopy or endoscopic or endoscopies)/ti,de
14. S (tomography or tomographies or pet(W)scan or pet(W)scans or pet(W)scanning)/ti,de
15. S (cat(W)scan or cat(W)scans or cat(W)scanning or ct(W)scan or ct(W)scans or ct(W)scanning)/ti,de
16. S (magnetic(W)resonance(W)imaging or mri or nmr(W)imaging or mr(W)imaging or chemical(W)shift(W)imaging)/ti,de
17. S (radiologic or radiological or radiologically or radiograph or radiography)/ti,de
18. S (flowcytometry or flow(W)cytometry or flowmetry or image(W)cytometry)/ti,de
19. S ((tumor or tumors or tumour or tumours or biologic or biological)(W)(marker or markers))/ti,de
20. S (diagnostic (W) (algorithm? or procedure? or rule or rules or tool or tools))/ti,de
21. S ((diagnosis or diagnostic or diagnostically) (3N) (efficient or efficiently or efficiency))/ti,de
22. S ((diagnosis or diagnostic or diagnostically) (3N) (efficacy or efficacies))/ti,de
23. S ((diagnosis or diagnostic or diagnostically) (3N) (accuracy or accurately or accurate))/ti,de
24. S ((diagnosis or diagnostic or diagnostically) (3N) (correct or corrects or correctly or corrected))/ti,de
25. S ((diagnosis or diagnostic or diagnostically) (3N) (reliable or reliability))/ti,de
26. S ((diagnosis or diagnostic or diagnostically) (3N) (error or errors))/ti,de
27. S ((diagnosis or diagnostic or diagnostically) (3N) (mistake or mistakes or mistaken or mistook))/ti,de

28. S ((diagnosis or diagnostic or diagnostically) (3N) (inaccurate or inaccurately or inaccuracy or inaccuracies))/ti,de
29. S ((diagnosis or diagnostic or diagnostically) (3N) (incorrect or incorrectly))/ti,de
30. S ((diagnosis or diagnostic or diagnostically) (3N) (unreliable or unreliability))/ti,de
31. S (reference (W) (test or tests or testing))/ti,de
32. S (sensitivity (3N) (test or tests))/ti,de
33. S (specificity (3N) (test or tests))/ti,de
34. S (predictive (w) (standard or standards or value or values or model or models or factor or factors))/ti,de
35. S (sroc or srocs or roc or rocs)/ti,de
36. S (receiver(W)operat?(W)curve or receiver(W)operat?(W)curves)/ti,de
37. S (receiver(W)operat?(W)Character or receiver(W)operat?(W)characteristic?)/ti,de
38. S (likelihood(W)ratio or likelihood(W)ratios)/ti,de
39. S (false(W)positive or false(W)positives or false(W)negative or false(W)negatives)/ti,de
40. S (true(W)negative or true(W)negatives or true(W)positive or true(W)positives)/ti,de
41. S (positive(W)rate or positive(W)rates or negative(W)rate or negative(W)rates)/ti,de
42. S ((accurate or accuracy or accuracies) (2N) (test or tests or testing))/ti,de
43. S ((accurate or accuracy or accuracies) (2N) (standard or standards))/ti,de
44. S ((accurate or accuracy or accuracies) (2N) (score or scores))/ti,de
45. S ((accurate or accuracy or accuracies) (2N) (aid or aids))/ti,de
46. S (reliable (2N) (test or tests or testing))/ti,de
47. S (reliable (2N) (standard or standards))/ti,de
48. S (reliability (2N) (test or tests or testing))/ti,de
49. S (reliability (2N) (standard or standards))/ti,de
50. S (performance (2N) (test or tests or testing))/ti,de
51. S (performance (2N) (standard or standards))/ti,de
52. S (misdiagnosis or misdiagnostic or misdiagnose)/ti,de
53. S s6 or s7 or s8 or s9 or s10 or s11 or s12 or s13 or s14 or s15 or s16 or s17 or s18 or s19 or s20 or s21 or s22 or s23 or s24 or s25 or s26 or s27 or s28 or s29 or s30 or s31 or s32 or s33 or s34 or s35 or s36 or s37 or s38 or s39 or s40
54. S s41 or s42 or s43 or s44 or s45 or s46 or s47 or s48 or s49 or s50 or s51 or s52
55. S s53 or s54
56. S s5 and s55

ISI Science Citation Index 1981–2003/26 October.
Accessed via Web of Knowledge (http://wok.mimas.ac.uk/)
Searched 28 October 2003. Retrieved 474 records.

1. (haematuria or hematuria or macrohematuria or macrohaematuria or microhematuria or microhaematuria)
2. ((blood cell* or red cell* or occult blood or rbc) same urin*)
3. #1 or #2
4. (urinalysis or urography or urographic or ivu or pyelography or pyelogram or pyelograms or ivp or ureteroscop* or cystoscop* or cystography or renal biopsy or renal biopsies or kidney biopsy or kidney biopsies)
5. (urin* culture* or urin* densit* or urin* sediment*)
6. (urin* cytolog* or urin* cytopath* or urin* microscop*)
7. (dipstick* or dip stick* or reagent strip* or test strip* or sediment* count*)
8. (xray* or x ray* or ultrasound or ultrasonograph* or endosonograph* or endoscop*)
9. (tomograph* or pet scan* or cat scan* or ct scan* or imaging or mri or nmr or mr or radiologic* or radiograph*)
10. (flowcytomet* or flow cytomet* or flowmetry or image cytomet*)
11. (tumor* marker* or tumour* marker* or biologic* marker*)
12. (diagnostic algorithm* or diagnostic procedure* or diagnostic rule* or diagnostic tool*)
13. #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12
14. #3 and #13
15. (diagnos* same (efficien* or efficacy* or effective* or accura* or correct* or reliable* or reliability or error* or mistake* or inaccura* or incorrect or unreliable))
16. (reference test* or sensitivity or specificity or predictive standard* or predictive value* or predictive model* or predictive factor*)
17. (sroc or srocs or roc or rocs)
18. (receiver operat* curve* or receiver operat* character*)
19. (likelihood ratio* or false positive* or false negative* or true negative* or true positive* or positive rate* or negative rate*)
20. (accura* same (test or tests or testing or standard* or score* or aid or aids))
21. (reliable* same (test or tests or testing or standard*))
22. (reliability same (test or tests or testing or standard*))

23. (performance same (test or tests or testing or standard*))
24. misdiagnos*
25. #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24
26. #3 and #25
27. #14 or #26
28. (animal or animals or dog or dogs or hamster* or mouse or mice or rat or rats or bovine or sheep or guinea*)
29. #27 not #28

Dissertation Abstracts 1861–2003/September.
Accessed via Dialog (file 35)
Searched 29 October 2003. Retrieved 4 records.

1. S (hematuria or haematuria)/ti,de
2. S (microhematuria or microhaematuria)/ti,de
3. S (macrohematuria or macrohaematuria)/ti,de
4. S ((blood(W)cell or blood(W)cells or red(W)cell or red(W)cells or occult(W)blood or rbc) (2W) (urine or urinary))/ti,de
5. S s1 or s2 or s2 or s4
6. S (urinalysis or urography or urographic or ivu or pyelography or pyelogram or pyelograms or ivp)/ti,de
7. S (ureteroscop? or cystoscop? or cystography)/ti,de
8. S (renal(2W)biopsy or renal(2W)biopsies or kidney(2W)biopsy or kidney(2W)biopsies)/ti,de
9. S ((urine or urinary) (2W) (culture or cultures or density or densities or sediment or sediments))/ti,de
10. S ((urine or urinary) (2W) (cytology or cytologies or cytopathology or cytopathologies or microscopy or microscopic or microscope))/ti,de
11. S (dipstick? or dip(W)stick? or reagent(W)strip or reagent(W)strips or test(W)strip or test(W)strips or sediment?(W)count or sediment?(W)counts)/ti,ab
12. S (xray or xrays or x(W)ray or x(W)rays or ultrasound)/ti,de
13. S (ultrasonography or endosonography or endoscopy or endoscopic or endoscopies)/ti,de
14. S (tomography or tomographies or pet(W)scan or pet(W)scans or pet(W)scanning)/ti,de
15. S (cat(W)scan or cat(W)scans or cat(W)scanning or ct(W)scan or ct(W)scans or ct(W)scanning)/ti,de
16. S (magnetic(W)resonance(W)imaging or mri or nmr(W)imaging or mr(W)imaging or chemical(W)shift(W)imaging)/ti,de
17. S (radiologic or radiological or radiologically or radiograph or radiography)/ti,de
18. S (flowcytometry or flow(W)cytometry or flowmetry or image(W)cytometry)/ti,de
19. S ((tumor or tumors or tumour or tumours or biologic or biological)(W)(marker or markers))/ti,de
20. S (diagnostic (W) (algorithm? or procedure? or rule or rules or tool or tools))/ti,de
21. S ((diagnosis or diagnostic or diagnostically) (3N) (efficient or efficiently or efficiency))/ti,de
22. S ((diagnosis or diagnostic or diagnostically) (3N) (efficacy or efficacies))/ti,de
23. S ((diagnosis or diagnostic or diagnostically) (3N) (accuracy or accurately or accurate))/ti,de
24. S ((diagnosis or diagnostic or diagnostically) (3N) (correct or corrects or correctly or corrected))/ti,de
25. S ((diagnosis or diagnostic or diagnostically) (3N) (reliable or reliability))/ti,de
26. S ((diagnosis or diagnostic or diagnostically) (3N) (error or errors))/ti,de
27. S ((diagnosis or diagnostic or diagnostically) (3N) (mistake or mistakes or mistaken or mistook))/ti,de
28. S ((diagnosis or diagnostic or diagnostically) (3N) (inaccurate or inaccurately or inaccuracy or inaccuracies))/ti,de
29. S ((diagnosis or diagnostic or diagnostically) (3N) (incorrect or incorrectly))/ti,de
30. S ((diagnosis or diagnostic or diagnostically) (3N) (unreliable or unreliability))/ti,de
31. S (reference (W) (test or tests or testing))/ti,de
32. S (sensitivity (3N) (test or tests))/ti,de
33. S (specificity (3N) (test or tests))/ti,de
34. S (predictive (w) (standard or standards or value or values or model or models or factor or factors))/ti,de
35. S (sroc or srocs or roc or rocs)/ti,de
36. S (receiver(W)operat?(W)curve or receiver(W)operat?(W)curves)/ti,de
37. S (receiver(W)operat?(W)Character or receiver(W)operat?(W)characteristic?)/ti,de
38. S (likelihood(W)ratio or likelihood(W)ratios)/ti,de
39. S (false(W)positive or false(W)positives or false(W)negative or false(W)negatives)/ti,de
40. S (true(W)negative or true(W)negatives or true(W)positive or true(W)positives)/ti,de
41. S (positive(W)rate or positive(W)rates or negative(W)rate or negative(W)rates)/ti,de
42. S ((accurate or accuracy or accuracies) (2N) (test or tests or testing))/ti,de
43. S ((accurate or accuracy or accuracies) (2N) (standard or standards))/ti,de
44. S ((accurate or accuracy or accuracies) (2N) (score or scores))/ti,de
45. S ((accurate or accuracy or accuracies) (2N) (aid or aids))/ti,de
46. S (reliable (2N) (test or tests or testing))/ti,de
47. S (reliable (2N) (standard or standards))/ti,de

48. S (reliability (2N) (test or tests or testing))/ti,de
49. S (reliability (2N) (standard or standards))/ti,de
50. S (performance (2N) (test or tests or testing))/ti,de
51. S (performance (2N) (standard or standards))/ti,de
52. S (misdiagnosis or misdiagnostic or misdiagnose)/ti,de
53. S s6 or s7 or s8 or s9 or s10 or s11 or s12 or s13 or s14 or s15 or s16 or s17 or s18 or s19 or s20 or s21 or s22 or s23 or s24 or s25 or s26 or s27 or s28 or s29 or s30 or s31 or s32 or s33 or s34 or s35 or s36 or s37 or s38 or s39 or s40
54. S s41 or s42 or s43 or s44 or s45 or s46 or s47 or s48 or s49 or s50 or s51 or s52
55. S s53 or s54
56. S s5 and s55

ISI Proceedings 1990–2003/26 October.
Accessed via Web of Knowledge (http://wok.mimas.ac.uk/)
Searched 28 October 2003. Retrieved 50 records.

1. (haematuria or hematuria or macrohematuria or macrohaematuria or microhematuria or microhaematuria)
2. ((blood cell* or red cell* or occult blood or rbc) same urin*)
3. #1 or #2
4. (urinalysis or urography or urographic or ivu or pyelography or pyelogram or pyelograms or ivp or ureteroscop* or cystoscop* or cystography or renal biopsy or renal biopsies or kidney biopsy or kidney biopsies)
5. (urin* culture* or urin* densit* or urin* sediment*)
6. (urin* cytolog* or urin* cytopath* or urin* microscop*)
7. (dipstick* or dip stick* or reagent strip* or test strip* or sediment* count*)
8. (xray* or x ray* or ultrasound or ultrasonograph* or endosonograph* or endoscop*)
9. (tomograph* or pet scan* or cat scan* or ct scan* or imaging or mri or nmr or mr or radiologic* or radiograph*)
10. (flowcytomet* or flow cytomet* or flowmetry or image cytomet*)
11. (tumor* marker* or tumour* marker* or biologic* marker*)
12. (diagnostic algorithm* or diagnostic procedure* or diagnostic rule* or diagnostic tool*)
13. #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12
14. #3 and #13
15. (diagnos* same (efficien* or efficacy* or effective* or accura* or correct* or reliable* or reliability or error* or mistake* or inaccura* or incorrect or unreliable))
16. (reference test* or sensitivity or specificity or predictive standard* or predictive value* or predictive model* or predictive factor*)
17. (sroc or srocs or roc or rocs)
18. (receiver operat* curve* or receiver operat* character*)
19. (likelihood ratio* or false positive* or false negative* or true negative* or true positive* or positive rate* or negative rate*)
20. (accura* same (test or tests or testing or standard* or score* or aid or aids))
21. (reliable* same (test or tests or testing or standard*))
22. (reliability same (test or tests or testing or standard*))
23. (performance same (test or tests or testing or standard*))
24. misdiagnos*
25. #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24
26. #3 and #25
27. #14 or #26
28. (animal or animals or dog or dogs or hamster* or mouse or mice or rat or rats or bovine or sheep or guinea*)
29. #27 not #28

SIGLE 1980–2003/6. Accessed via ARC2 WebSPIRS
Searched 29 October 2003. Retrieved 5 records.

1. hematuria or haematuria
2. microhematuria or microhaematuria
3. macrohematuria or macrohaematuria
4. (blood cell* or red cell* or occult blood) near2 urin*)
5. or/1-5

LILACS 1982–2003. Accessed via BVS Virtual Health Library (http://bases.bireme.br/cgi-bin/wxislind.exe/iah/online/)
Searched 14 November 2003. Retrieved 178 records.

hematuria or haematuria or microhematuria or microhaematuria or macrohematuria or macrohaematuria {words}

AND
urinalys$ or urograph$ or ivu or pyelograph$ or pyelogram$ or ivp or ureteroscop$ or cystoscop$ or cystography or biops$ or culture$ or densit$ or sediment$ or cytolog$ or cytopath$ or microscop$

or dipstick$ or dip stick$ reagent strip$ or test strip$ or xray$ or x ray$ or ultrasound or ultrasonograph$ or endosonograph$ or endoscop$ or tomograph$ or cat scan$ or pet scan$ or ct or imaging or mri or radiologic$ or radiograph$ or flowcytomet$ or flow cytomet$ or flowmetry or image cytomet$ or tumor$ marker$ or tumour$ marker$ or biologic$ marker$ or diagnostic algorithm$ or diagnostic procedure$ or diagnostic rule$ or diagnostic tool$ {words}

hematuria or haematuria or microhematuria or microhaematuria or macrohematuria or macrohaematuria {words}
AND
"sensitivity$ and specificity" or "predictive value of tests" or or "logistic models" or 'likelihood functions' or "diagnostic errors" {subject descriptor}

hematuria or haematuria or microhematuria or microhaematuria or macrohematuria or macrohaematuria {words}
AND
diagnos$ efficien$ or diagnos$ efficac$ or effective$ diagnos$ accura$ diagnos$ or correct$ diagnos$ or reliable diagnos$ or diagnos$ error$ or diagnos$ mistake$ or inaccura$ diagnos$ or incorrect diagnos$ or unreliable diagnos$ or reference test or reference tests or reference testing or predictive standard$ or predictive value$ or predictive model$ or predictive factor$ {words}

hematuria or haematuria or microhematuria or microhaematuria or macrohematuria or macrohaematuria {words}
AND
sroc or srocs or roc or rocs or receiver operat$ curve$ or receiver operat$ character$ or likelihood ratio$ or false positive$ or false negative$ or true negative$ or true positive$ or positive rate$ or negative rate$ or accura$ test or accura$ tests or accura$ testing or accura$ standard$ or accura$ score$ or accura$ aid or accura$ aids or reliab$ test or reliab$ tests or reliab$ testing or reliab$ standard$ or test performance or tests performance or testing performance or standard$ performance or misdiagnos$ {words}

National Research Register (NRR) Issue 3 2003. Accessed via Update Software (http://www.update-software.com/nrr) Searched 4 November 2003. Retrieved 30 records.

#1 HEMATURIA*:ME
#2 (((((HEMATURIA or HAEMATURIA) or MICROHEMATURIA) or MICROHAEMATURIA) or MACROHAEMATURIA) or MACROHEMATURIA)
#3 ((OCCULT next BLOOD) near URIN*)
#4 ((BLOOD next CELL) near URIN*)
#5 ((RED next CELL*) near URIN*)
#6 ((((#1 or #2) or #3) or #5) or #6)

MetaRegister of Current Controlled Trials (mRCT). Accessed via www.controlled-trials.com Searched 28 November 2003. Search engine looks for alternative spellings. Terms searched separately. Retrieved 0 records.

Hematuria! or macrohematuria! or microhematuria!
Blood and urin%
Rbc and urin%

NTIS (National Technical Information Service) 1990–2003. Accessed via US Department of Commerce (www.ntis.gov) Searched 28 November 2003. Each line searched separately. Retrieved 2 records.

Hematuria or haematuria or macrohematuria or macrohaematuria or microhematuria or microhaematuria
'blood cell' and urine
'blood cell' and urinary
'blood cell' and urinalysis
'red cell' and urine
'red cell' and urinary
'red cell' and urinalysis
rbc and urine
rbc and urinary
rbc and urinalysis
"blood in the urine"

GrayLIT Network. Accessed via Office of Scientific and Technical Information (http://graylit.ost.gov)
Searched 28 November 2003. Each line searched separately. Retrieved 1 record.

Hematuria or haematuria or macrohematuria or macrohaematuria or microhematuria or microhaematuria
Blood and urine
Blood and urinary
Blood and urinalysis
Rbc and urine
Rbc and urinary
Rbc and urinalysis

OMNI (Organising Medical Networked Information). Accessed via http://omni.ac.uk
Searched 28 November 2003. Retrieved 0 records.
Each line searched separately, Automatic truncation.

Hematuria or haematuria or microhematuria or microhaematuria or macrohematuria or macrohaematuria
Blood and urin
Rbc and urin

Google Search Engine. Accessed via www.google.co.uk Searched 1 and 2 December 2003. Each line searched separately. Retrieved 11 records.

Haematuria "diagnostic technique"
Hematuria "diagnostic technique"
Haematuria "diagnostic algorithm"
Hematuria "diagnostic algorithm"
Haematuria "diagnostic procedure"
Hematuria "diagnostic procedure"
Haematuria "diagnostic rule"
Hematuria "diagnostic rule"
Haematuria " diagnostic tool"
Hematuria "diagnostic tool"
Haematuria "diagnostic test"
Hematuria "diagnostic test"

NHS EED (NHS Economic Evaluations Database) 1985–2003/12.
Searched via Internal CAIRS T system
Searched 9 December 2003. Retrieved 35 records.

S hematuria or haematuria or microhematuria or microhaematuria or macrohematuria or macrohaematuria
S ((blood(w)cell$ or red(w)cell$ or occult(w)blood or rbc)adj2 urin$)
S s1 or s2

OHE HEED (Office of Health Economics Health Economics Evaluations Database) 1985–2003/12.
Accessed via CD-ROM.
Searched 9 December 2003. Retrieved 14 records.

AX= hematuria or haematuria
AX=microhematuria or microhaematuria
Ax= macrohematuria or macrohaematuria
Ax= 'blood cell' and urin*
Ax= 'blood cells' and urin*
Ax= 'red cell' and urin*
Ax= 'red cells'and urin*
Ax= 'occult blood' and urin*
Ax= rbc and urin*

Economics Working Paper Archive (Economics Department, University of Washington).
Accessed via http://econwpa.wustl.edu
Accessed 17 December 2003. No search engine available – browsed pages. Retrieved 0 records.

Additional searches were carried out for economic models for bladder cancer and quality of life for superficial bladder cancer.

Economics: Markov/models strategy

Database: Ovid MEDLINE 1966 to March Week 4 2004. Accessed via Ovid web (http://gateway1.uk.ovid.com/ovidweb.cgi)
Search date: 1 April 2004

1 Bladder Neoplasms/
2 bladder cancer$.ti,ab.
3 neobladder.ti,ab.
4 bladder neoplas$.ti,ab.
5 bladder carcinoma.ti,ab.
6 locally advanced bladder.ti,ab.
7 metastatic bladder.ti,ab.
8 meta-static bladder.ti,ab.
9 advanced bladder.ti,ab.
10 bladder transitional cell.ti,ab.
11 bladder tumo?r.ti,ab.
12 or/1-11
13 exp models economic/
14 *models theoretical/
15 *models organizational/
16 economic model$.tw.
17 markov chains/
18 markov$.tw.
19 monte carlo method/
20 monte carlo.tw.
21 exp decision theory/
22 -(decision$ adj2 (tree$ or analy$ or model$)).tw.
23 or/13-22
24 12 and 23

Economics: Quality of life strategies

Database: Ovid MEDLINE 1966 to March Week 4 2004. Accessed via Ovid web (http://gateway1.uk.ovid.com/ovidweb.cgi
Search date: 7 April 2004.

1 (superficial adj2 bladder).mp.
2 sbc.tw.

3 1 or 2
4 Quality of Life/
5 Health Status Indicators/
6 Quality-Adjusted Life Years/
7 (qaly or quality adjusted life or quality of life or life quality).tw.
8 (quality of wellbeing or quality of well being).tw.
9 qwb$.tw.
10 health status.tw.
11 health related quality of life.tw.
12 rosser.tw.
13 (sf36 or sf 36).tw.
14 (short form 36 or short form 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortfrom thirty six or short form thirtysix or short form thirty six).tw.
15 (hrql or hrqol or h qol or hql or hqol).tw.
16 (eq5d or eq 5d or euroqol or euro qol).tw.
17 (qlq c30 or qlqc30 or qlq bls24 or qlqbls24 or eortc or fact bl or factbl).tw.
18 (hye or hyes or health$ year$ equivalent$ or health utilit$).tw.
19 (Standard gamble$ or time trade off or time tradeoff or tto or willingness to pay).tw.
20 functional assessment of cancer therapy.tw.
21 sickness impact profile.tw.
22 "Sickness Impact Profile"/
23 or/4-22
24 3 and 23

Database: EMBASE 1980 to 2004 week 14.
Accessed via Ovid web
(http://gateway1.uk.ovid.com/ovidweb.cgi
Search date: 7 April 2004

1 (superficial adj2 bladder).mp.
2 sbc.tw.
3 1 or 2
4 Quality of Life/
5 Health Status Indicators/
6 health survey/
7 Quality Adjusted Life Year/
8 (qaly or quality adjusted life or quality of life or life quality).tw.
9 (quality of wellbeing or quality of well being).tw.
10 qwb$.tw.
11 health status.tw.
12 health related quality of life.tw.
13 rosser.tw.
14 (sf36 or sf 36).tw.
15 (short form 36 or short form 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortfrom thirty six or short form thirtysix or short form thirty six).tw.
16 (hrql or hrqol or h qol or hql or hqol).tw.
17 (eq5d or eq 5d or euroqol or euro qol).tw.
18 (qlq c30 or qlqc30 or qlq bls24 or qlqbls24 or eortc or fact bl or factbl).tw.
19 (hye or hyes or health$ year$ equivalent$ or health utilit$).tw.
20 (Standard gamble$ or time trade off or time tradeoff or tto or willingness to pay).tw.
21 functional assessment of cancer therapy.tw.
22 sickness impact profile.tw.
23 "Sickness Impact Profile"/
24 or/4-23
25 3 and 24

Update searches using the strategies listed above were completed on 29 July 2004

MEDLINE 2003/October week 3–2004/July week 3. Accessed via Ovid web
(http://gateway1.uk.ovid.com/ovidweb.cgi)
Searched 29 July 2004. Retrieved 250 records.

EMBASE 2003/week 42–2004/week 30. Accessed via Ovid web
(http://gateway2.uk.ovid.com/ovidweb.cgi.)
Searched 29 July 2004. Retrieved 354 records.

BIOSIS 2003/October week 3 – 2004/July. accessed via Dialog (file 5)
Searched 29 July 2004. Retrieved 140 records.

Pascal 2003/October week 3–2004/July. Accessed via Dialog (file 144) searched 29.07.04. Retrieved 17 records.

ISI Science Citation Index 2003/
26 October–2004/29 July.
Accessed via Web of Knowledge
(http://wok.mimas.ac.uk/)
Searched 29 July 2004. Retrieved 235 records.

Dissertation Abstracts 2003/September–2004/July.
Accessed via Dialog (file 35)
Searched 29 July 2004. Retrieved 0 records.

ISI Proceedings 2003/26 October–2004/29 July.
Accessed via Web of Knowledge
(http://wok.mimas.ac.uk/)
Searched 29 July 2004. Retrieved 24 records.

SIGLE 2003/6–2003/12. Accessed via ARC2 WebSPIRS
Searched 29 July 2004. Retrieved 0 records.

LILACS 2003–2004. Accessed via BVS Virtual Health Library

(http://bases.bireme.br/cgi-bin/wxislind.exe/iah/online/)
Searched 29 July 2004. Retrieved 7 records.

National Research Register (NRR) Issue 3 2003–Issue 2 2004. Accessed via Update Software (http://www.update-software.com/nrr)
Searched 29 July 2004. Retrieved 2 records.

MetaRegister of Current Controlled Trials (mRCT). Accessed via www.controlled-trials.com
Searched 29 July 2004. Search engine looks for alternative spellings. Terms searched separately. Retrieved 0 records.

NTIS (National Technical Information Service) 2003–2004
Accessed via US Department of Commerce (www.ntis.gov)
Searched 29 July 2004. Each line searched separately. Retrieved 0 records.

GrayLIT Network
Accessed via Office of Scientific and Technical Information (http://graylit.ost.gov) Searched 29 July 2004. Retrieved 0 records.

OMNI (Organising Medical Networked Information). Accessed via http://omni.ac.uk
Searched 29 July 2004. Retrieved 0 records.

Google Search Engine Accessed via www.google.co.uk
Searched 29 July 2004. Each line searched separately. Retrieved 0 records.

NHS EED (NHS Economic Evaluations Database) 2003/12–2004/6. Searched via Internal CAIRS T system. Searched 29 July 2004. Retrieved 3 records.

OHE HEED (Office of Health Economics Health Economics Evaluations Database) 2003/12–2004/7. Accessed via CD-ROM.
Searched 29 July 2004. Retrieved 2 records.

Economics Working Paper Archive (Economics Department, University of Washington). Accessed via http://econwpa.wustl.edu
Accessed 29 July 2004. No search engine available. Pages browsed. Retrieved 0 records.

Handsearch

The date of last search was 3 September 2004.

The search comprised the following:

1. *Journal of Urology, British Journal of Urology, Deutsche Medizinische Wochenschrift, Nephron, Nephron: Clinical Praxis* and *Urology* from 2000 to date and forthcoming if available. The *Nephron* subjournals were also searched as they seem more or less to replace the main journal from 2003 onwards: *Nephron: Experimental Nephrology* and *Nephron: Physiology* were searched from the start of the subjournals in 2003 to date and forthcoming where available.
2. The June, July and August issues and any available forthcoming issue or article of *American Journal of Clinical Pathology*, *Clinical Nephrology journal*, *British Journal of Radiology*, *Lancet*, *JAMA* and the *BMJ* were searched, complementing the electronic searches to obtain recently published articles.
3. The search included regular journal issues and also supplements where available (and which are not necessarily indexed in MEDLINE).
4. The search comprised abstracts of the following conferences:
   (a) ESPU/AAP Meeting, June 2000
   (b) a conference published in October 2000
   (c) Annual Scientific Meeting of the British Association of Urological Surgeons, 25–28 June 2001
   (d) Urological Research Society Annual Scientific Meeting, 5 January 2001
   (e) Annual Scientific Meeting 2002 published in *British Journal of Urology*
   (f) 26th SIU, Stockholm, 8–12 September 2002
   (g) XIVth ESPU, Madrid, 12–15 March 2003
   (h) British Association of Urological Surgeons (BAUS) Annual Meeting, Manchester, 23–27 June, 2003
   (i) XV ESPU, Regensburg, 21–24 April 2004
   (j) BAUS Annual Meeting, Harrogate, 21–25 June 2004
   (k) American Urological Association meeting, San Francisco, 2004.

Search details of the handsearch

Key journals judging from the journal topic were searched, in addition to journals identified during the review as having contributed the most articles eligible for inclusion in the review.

American Journal of Clinical Pathology (AJCP)
Access: http://ajcp.metapress.com/app/home/journal.asp?wasp=ecxx5uwuyn6jwwevkyvm&referrer=parent&backto=browsepublicationsresults,1,2
June–October 2004.

Clinical Nephrology
Access: http://www.dustri.com/ze/cn/31cnlink.htm

June, **61**, No. 6/2004–August, **62**, No. 2/2004 (September volume not yet available).

British Journal of Radiology
Access:http://www.ingenta.co.uk/isis/browsing/TOC/ingenta?issue=pubinfobike://bir/bjr/2004/00000077/00000920
June, **77**, 918–August, **77**, 920, 2004
Current August edition
Directly from publisher: http://bjr.birjournals.org/.

Lancet
Access: http://www.sciencedirect.com/science?_ob=JournalURL&_cdi=4886&_auth=y&_acct=C000010338&_version=1&_urlVersion=0&_userid=126317&md5=811e0f08d3ddd876d6c51674ee68a2ce
Searched June to September 2004
Early online publication and available supplements
Access directly from the publisher: http://www.thelancet.com/journal.

JAMA
Access: http://jama.ama-assn.org/
June **291**, 21 – September **292**, 9
Student *JAMA*, *JAMA* express, Early released articles 3 September also searched.

BMJ
Access: http://bmj.bmjjournals.com/
June 328, 7452 – September **329**, 7465, 2004
Press releases and online first 3 September searched.

Urology
Access: http://www.sciencedirect.com/
2000 **55** to date (3 September 2004), including supplements
Articles in press 3 September
Access:http://www.sciencedirect.com/science?_ob=JournalURL&_cdi=6105&_auth=y&_acct=C000010338&_version=1&_urlVersion=0&_userid=126317&md5=b763da7831308374ad71cae255f68294.

Journal of Urology
Access:http://www.jurology.com/pt/re/juro/home.htm;jsessionid=Bc5mTBweT26rU1AfleTMijkqPOhoCyKuiHacAZGxmlArkHiDKQTR!-898954818!-949856032!9001!-1
2000 **163** to date (3 September 2004: **172**, September), including supplements.

Nephron and subjourals
Including supplements and forthcoming papers
Access:
http://content.karger.com/ProdukteDB/produkte.asp?Aktion=BackIssues&ProduktNr=223854
2000 **84** to date (3 September 2004).
Subjournal *Nephron: Clinical Praxis*
2000 to date (3 September 2004).
Subjournal *Nephron: Experimental Nephrology*
2003 (start of journal) to date (3 September 2004)
Subjournal *Nephron: Physiology*'
2003 (start of journal) to date (3 September 2004)

Deutsche Medizinische Wochenschrift (DMW)
Access via ISI Web of Knowledge:
http://portalt.wok.mimas.ac.uk/portal.cgi?DestApp=WOS&Func=Frame
2000 to date (3 September 2004)
Current issue (August)
Access via publisher: http://www.thieme-connect.de/ejournals/toc/dmw
Forthcoming papers not accessible.

British Journal of Urology – BJU International
Access: http://www.bjui.org/index.asp?bjupage=issues&open=2000&open=2004
2000 **85** to date (3 September 2004, August) including supplements (conference abstracts); no forthcoming papers available.

Appendix 3

QUADAS and details of criteria for scoring studies

QUADAS[38]

1.	**Was the spectrum of patients representative of the patients who will receive the test in practice**?
Yes	Diagnosis: patients in whom haematuria is suspected Further investigation: patients with confirmed haematuria
No	All other patient spectrums including retrospectively selected patient spectrums and mixed populations
Unclear	If insufficient details are provided to make a judgement as to whether the patient spectrum would be scored as 'yes'

2.	**Were selection criteria clearly described?**
Yes	Enough details are provided of how patients were selected so that the selection process could be replicated
No	Insufficient details are presented
Unclear	Not applicable

3.	**Is the reference standard likely to classify the target condition correctly?**
Yes	Diagnosis: microscopy Further investigation: cystoscopy for bladder tumours, biopsy for renal tumours
No	All other reference standards
Unclear	If details of the reference standard are not reported

4.	**Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?**
Yes	Diagnosis: should be performed on the same sample of urine Further investigation: tests performed < 1 week apart
No	If not as above
Unclear	If details are not reported

5.	**Did the whole sample, or a random selection of the sample, receive verification using a reference standard of diagnosis?**
Yes	If the whole sample or a random selection of the sample received a reference standard of diagnosis
No	If only a selected sample received the reference standard
Unclear	If it is not clear whether all the patients received the reference standard

6.	**Did patients receive the same reference standard regardless of the index test result?**
Yes	If all patients received the same reference standard
No	If some patients received a different reference standard
Unclear	If it is not clear whether all patients received the same reference standard

7.	**Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?**
Yes	If the index test and reference standard were independent
No	If the index test formed part of the reference standard
Unclear	If it is not clear if the index test and reference standard were independent

8a.	**Was the execution of the index test described in sufficient detail to permit replication of the test?**
8b.	**Was the execution of the reference standard described in sufficient detail to permit its replication?**
Yes	If sufficient details of test execution are reported
No	If sufficient details are not reported
Unclear	Not applicable

9a.	**Were the index test results interpreted without knowledge of the results of the reference standard?**
9b.	**Were the reference standard results interpreted without knowledge of the results of the index test?**
Yes	If the index test was interpreted without knowledge of the results of the reference standard and vice versa. If one test was clearly interpreted before the results of the other test were available then this should be scored as 'yes'
No	If the person interpreting the index test was aware of the results of the reference standard or vice versa
Unclear	If no information is provided regarding whether tests were interpreted blindly

10.	**Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?**
Yes	History and examination, including haematuria
No	If not as above
Unclear	If details on the availability of clinical data are not reported

11.	**Were uninterpretable/intermediate test results reported?**
Yes	If details are provided on uninterpretable/ intermediate test results
No	If there appear to be some uninterpretable/intermediate test results but the results of these are not reported
Unclear	If it is not clear whether there were any uninterpretable/intermediate test results

12.	**Were withdrawals from the study explained?**
Yes	If all patients recruited into the study were accounted for
No	If there appear to be patients who were recruited into the study who are not accounted for
Unclear	If it is not clear whether any withdrawals occurred

Appendix 4

Included studies: diagnosis of haematuria

Study details	Participants	Index test	Index test cut-off	Reference standard(s)	Reference standard cut-off
Arm (1986)[49]	Query haematuria (patients routinely admitted, selected on the basis of a knowledge or suspicion that haematuria was present)	Dipstick (N-Multistix-SG, Ames)	Trace, +, ++ or +++	Microscopy [microscopy (PCM) of urine sediment (uncentrifuged), counted by haemocytometer. Two counts of each specimen were made]	≥10 RBCs/μl
Bonard (1986)[50]	Population screening	Dipstick (N-Multistix, Ames) Dipstick read on an automatic reader (Ames-Clini-Tek)		Microscopy [microscopy of urine sediment (centrifuged)]	≥10 RBCs/μl
Bove (1999)[68]	Other (patients with acute flank pain referred from emergency department)	Haematuria. Dipstick; Microscopy of urine sediment (centrifuged). 400 × magnification	>5 RBCs/hpf >1 RBC/hpf Any RBCs >1 RBC/hpf or positive dipstick	Unenhanced helical CT	Presence of utererolithiasis
Braun (1975)[51]	Population screening (ambulant patients)	Dipstick (Sangur-Test, Boehringer Mannheim)	Any RBCs > 5 RBCs/μl	Microscopy [microscopy of urine sediment (centrifuged). 320× magnification, 10 hpf examined. Quantitative calculation in Fuchs–Rosenthal chamber of uncentrifuged urine]	>5 RBCs/hpf
Demol (1980)[52]	Population screening (medical emergency admissions)	Dipstick (Bili-Labstix, Ames)		Microscopy [microscopy of urine sediment (uncentrifuged). 400× magnification]	≥10 RBCs/hpf
Freeland (1987)[69]	Other	Haematuria (dipstick haematuria, Ames)	Non-haemolysed trace to 3+	IVU and visual examination of urine (urine was passed through Whatman No. 1 filter paper, which was then inspected for evidence of calculi)	Urinary calculi present
Froom (1987)[53]	Population screening (asymptomatic airforce crewmen)	Other (microscopy (hpf)]. Microscopy of urine sediment (centrifuged). 400× magnification, 10–20 hpf examined	≥1 RBC/hpf ≥3 RBCs/hpf	Microscopy [microscopy of urine sediment (uncentrifuged), counted by haemocytometer. The average number of RBCs was calculated from 3 × 0.9 mm^3 fields]	>2000 RBCs/ml >5000 RBCs/ml

continued

Study details	Participants	Index test	Index test cut-off	Reference standard(s)	Reference standard cut-off
Gibson (1986)[54]	Other (inpatients, including some with known haematuria following urological procedures)	Dipstick (Multistix, Ames)	>Trace	Microscopy [microscopy of urine sediment (uncentrifuged), counted by haemocytometer. 40× magnification. Two counts of each specimen were made]	$\geq 10^6$ cells/l
Gleeson (1993)[55]	Other (urology outpatients)	Dipstick (B.M. test, Boehringer Mannheim)	Trace, 1+, 2+. 3+ or 4+	Microscopy [microscopy of urine sediment (uncentrifuged)]	≥5 RBCs/μl
Grinstead (1987)[56]	Other	Dipstick (Clinitek 200/Multistix 9, Ames)	≥Trace	Microscopy [microscopy of urine sediment (centrifuged). 400× magnification]	≥1 RBC/hpf ≥4 RBCs/hpf
Gruhn (1974)[57]	Other (nephrology, urology and gynaecology patients)	Dipstick (N-Labstix, Ames)		Other (Reagnost tablets)	Presence of haemoglobin
Holland (1995)[58]	Other (mixed inpatients and outpatients)	Dipstick [Multistix-10 (read visually), Ames]. Strips were read visually using colour-change guidance charts. Dipstick [Multistix-10 (read by photometry), Ames]. Strips were read by reflectance photometry in a semi-automated urine chemistry analyser machine (Clinitek-100, Ames). Dipstick [Combur-10 (read visually), Boehringer Mannheim]. Strips were read visually using colour-change guidance charts		Microscopy [microscopy of urine sediment (uncentrifuged), counted by haemocytometer. The number of RBCs was graded as <10, 10–100 or >100 million per litre]	$\geq 10^6$ cells/l

continued

Study details	Participants	Index test	Index test cut-off	Reference standard(s)	Reference standard cut-off
Jaffe (1979)[59]	Other (patients providing samples for routine urinalysis)	Dipstick (Multistix, Ames)	Slight (1+), moderate (2+) or marked (3+) haematuria	Microscopy [microscopy of urine sediment (centrifuged). 450× magnifcation, ≥ 10 hpf examined]	>20 RBCs/hpf >1 RBC/hpf >5 RBCs/hpf
Kutter (1974)[61]	Population screening (urine samples from daily routine)	Dipstick (Sangur-Test, Boehringer Mannheim)		Microscopy (microscopy sediment method)	
Kutter (1980)[60]	Unclear (mainly inhabitants of residential homes for the elderly)	Dipstick (Combur-8, Boehringer Mannheim)	Any RBCs	Microscopy (microscopy of urine sediment. MD-KOVA system)	≥5 RBCs
McGlone (1990)[62]	Query haematuria (patients presenting to the accident and emergency department with abdominal pain)	Dipstick (Ames SG10, Ames)		Microscopy [microscopy of urine sediment (uncentrifuged). 400× magnification]	Any RBCs
Messing (1987)[63]	Other (urology outpatients)	Dipstick	≥ Trace	Microscopy [microscopy of urine sediment (centrifuged). 400× magnification, 20 hpf examined]	≥2 RBCs/hpf
Ooi (1998)[64]	High risk (e.g. known renal or oncology patients) (patients presenting to an emergency department with loin or loin to groin pain)	Dipstick (Combur 9, Boehringer Mannheim) Microscopy of urine sediment (uncentrifuged)	≥ 1 RBC or haemoglobin >5 RBC/hpf for males, >10 RBC/hpf for females	Microscopy [microscopy of urine sediment (uncentrifuged)] KUB and IVU, or calculi passed (in patients who did not attend for IVU or whose initial KUB suggested calculi but the IVU was reported as negative, telephone interviews were conducted at least 6 months after testing to determine whether calculi had been passed)	>5 RBCs/hpf for males, and >10 RBCs/hpf for females. Urinary calculi present
Parekattil (2003)[70]	Other (urology patients undergoing cystoscopic evaluation)	Dipstick	Presence of haematuria	Cystoscopy (cystoscopy, bladder cancer confirmed by biopsy)	Presence of bladder tumour

continued

Study details	Participants	Index test	Index test cut-off	Reference standard(s)	Reference standard cut-off
Safriel (2003)[71]	Other (patients presenting to the emergency department with acute abdominal colic and a clinical suspicion of urinary calculi)	Microscopy	≥2 RBCs/hpf (on 2 occasions)	CT (CT scanning was performed using spiral technique at 5mm collimation and a pitch of 1.5 on a GE Cti (General Electric, Milwaukee, WI, USA). Initially without contrast and repeated with contrast as indicated)	Urinary calculi present
Sanchez Carbayo (2000)[72]	High risk (e.g. known renal or oncology patients) [patients 'at risk' for bladder cancer (under suspicion of a primary bladder tumour or follow-up of a previous bladder tumour)]	Microhaematuria	Presence of microhaematuria	Cystoscopy	Presence of bladder tumour
Shaw (1985)[65]	Population screening (outpatients)	Dipstick (Multistix, Ames) Dipstick (Chemstrip 9, Bio-Dynamics)	Trace, 1+, or 2+. ≥1 RBC 2+ RBCs	Microscopy [microscopy of urine sediment (centrifuged). 100× magnification for casts and 400× magnification for cells]	≥1 RBC/hpf. Any RBCs
Wawroschek (1998)[66]	High risk (e.g. known renal or oncology patients) (patients with carcinoma of the urinary bladder)	Dipstick (Combur 9, Boehringer Mannheim) The strip is dipped into the urine and compared with a colour scheme after 1 minute		Microscopy [microscopy of urine sediment (centrifuged). MD-KOVA system. 400× enlargement]	>3 RBCs/hpf
Yoo (1995)[67]	Other (mixed inpatients and outpatients)	Dipstick (Uriflet, Kyoto Daiichi Kagaku)	> +	Microscopy [microscopy of urine sediment (centrifuged). Stained with or without a modified Sternheimer solution]	>5 RBCs/hpf

Appendix 5

Included studies: further investigation to determine the underlying cause of haematuria

Study details	Participants	Index test	Index test cut-off	Reference standard(s)	Reference standard cut-off
Ahmad (1993)[73]	Other (patients with 'significant' haematuria (>13000 RBCs/ml))	PCM, urinary RBC morphology (centrifuged urine sample examined at 400× magnification)	*Glomerular*: urinary RBCs showing a wide range of variation, frequently with loss of haemoglobin. Non-glomerular and mixed are classified as negative *Non-glomerular*: RBCs morphologically uniform with not more than two cell populations present. Glomerular and mixed are classified as negative	Final diagnosis (radiology, cystoscopy, renal biopsy)	Glomerulonephritis proven by renal biopsy
Akaza (1997)[29]	Other (patients with microscopic haematuria)	NMP22 marker Urine cytology (measurement was carried out using MSU)	12.0 U/ml. Papanicolau classification class IV and V (I, II and III as negative)	Cystoscopy	Diagnosis of urothelial cancer
Andreev (1995)[74]	Patients with haematuria (>8 RBCs/hpf)	PCM, urinary RBC morphology (centrifuged urine sample. The phase contrast microscope had a magnification of 400×. The authors looked for 5 types of dysmorphe erythrocytes: ring form akanthozyt, codozyt, knizozyt and stomatozyt)	*Glomerular*: ≥15% of dysmorphic RBCs	Previously established diagnosis (clinical, histological, instrumental or other laboratory procedure)	Diagnosis of glomerular disease

continued

Study details	Participants	Index test	Index test cut-off	Reference standard(s)	Reference standard cut-off
Apeland (1995)[76]	Other (patients with unexplained haematuria)	Technicon (Belgium) urinary RBC volume and density Autoanalyser (flow cytometry) [centrifuged urine sample, re-suspended and 1-ml aliquots diluted with the standard Technicon reagents RBC dil and HGB dil. These dilutents give information about urinary erythrocytes and debris and haemolysed erythrocytes, respectively. Analyses were performed using the Technicon H-1 system in the direct cytometry mode and with the direct RBC option (analysed within 6 hours of voiding)]	*Glomerular*: index value <1. The index value was defined as: test index = {count area 1(RBC dil) – count area 1(HGB dil)]/[count area 2(RBC dil) – count area 2(HGB dil)}	Final diagnosis (renal biopsy was performed in 37 cases. No further details were reported)	Glomerular cause of haematuria diagnosed
Apeland (2001)[75]	Other (patients with a well-defined single cause of dipstick haematuria)	Sysmex UF-100, GMBH Europe, Hamburg, Germany; urinary RBC size (uncentrifuged urine sample) Olympus BH-2 Bright-field, using Sternheimer–Malbin stain (centrifuged urine sample, examined at 100× and 400× magnification)	*Glomerular*: >80% of RBC volumes ≥ 126 channels and <80% to ≥ 84 channels. Additional criteria applied to mixed picture samples: presence of increased numbers of small round cells (i.e. mostly renal tubular cells) or pathological casts made renal bleeding more likely. Presence of high levels of leucocytes, bacteria or yeast indicated a non-glomerular disorder	Previously established diagnosis	Established glomerular disease

continued

Study details	Participants	Index test	Index test cut-off	Reference standard(s)	Reference standard cut-off
Aslaksen (1990)[120]	Other (patients with microscopic haematuria, referred for IVU)	Ultrasound (ultrasound was performed using a real-time scanner with a 5-MHz sector phased array transducer. Examinations were conducted in the supine and oblique position, preferably with a full bladder and recorded on video tape to allow review)	Tumour of the urinary tract. Renal or ureteric calculi, defined as hyperechoic foci with a well-defined acoustic shadow. Suspected calculi with a diameter of 2 mm or less were not reported as positive findings	IVU (performed with compression with an initial 24 × 30 cm zonogram over the kidney region, followed by a 35 × 43 cm film covering the kidneys and bladder. Further radiograms were obtained in patients with impaired renal function due to obstruction. Metrizoate (Isopaque, Nycomed, 440 mg iodine/ml) was used as the standard contrast medium in 177 patients, Iohexol (Omnipaque, Nycomed, 300 mg iodine/ml) was used in 14 patients and Ioxaglate (Hexobrix, Guerbet, 320 mg iodine/ml) in two patients with additional risks, e.g. allergy or heart failure	Detection of a tumour of the urinary tract. Detection of renal or ureteric calculi
Banks (1989)[77]	Query haematuria [patients with dipstick haematuria (≥ 1+)]	Coulter S + III Urinary RBC volume (centrifuged urine sample, 44.7 µl re-suspended in Isoton and analysed for MCV using the predilution mode. If RBC numbers were insufficient to produce a smooth frequency distribution curve, a further 44.7 µl were added)	*Glomerular*: mean corpuscular volume of urinary RBCs <80 fl	Final diagnosis (renal biopsy, cystoscopy or radiology)	Diagnosis of a glomerular disease
Birch (1983)[78]	Haematuria (patients referred to nephrology for investigation of microhaematuria)	PCM, urinary RBC morphology	*Glomerular*: dysmorphic changes in RBCs *Non-glomerular*: defined as negative: RBCs morphologically normal, with not more than 2 cell populations present	Final diagnosis (tests including renal biopsy, IVU, antegrade or retrograde pyelography, renal arteriography and cystoscopy)	Not reported

continued

Study details	Participants	Index test	Index test cut-off	Reference standard(s)	Reference standard cut-off
de Caestecker (1992)[79]	Other (patients with dipstick haematuria, and an established clinical diagnosis)	Coulter ZF6 Urinary RBC volume (sample preparation included serial dilutions of uncentrifuged samples to identify the effects of particulate interference, additional analyses of resuspended centrifuged samples to improve conductivity, and repeat analysis following addition of a haemolysing reagent to differentiate erythrocytes from other cellular components and background debris. Modal values were derived from volume frequency histograms)	*Glomerular*: modal volume 30–59 fl, where modal volumes were derived from volume frequency histograms. Non-glomerular and mixed are classified as negative. *Non-glomerular*: modal volume 60–180 fl, where modal volumes were derived from volume frequency histograms. Glomerular and mixed are classified as negative	Previously established diagnosis	Established glomerular disease
Catala Lopez (2002)[80]	Other [patients with haematuria (>10 RBCs/hpf)]	PCM, urinary RBC morphology PCM, acanthocyte count (centrifuged urine sample. Ten fields and at least 100 erythrocytes were counted)	*Glomerular*: ≥ 35% dysmorphic RBCs. *Glomerular*: ≥ 5% acanthocytes	Previously established diagnosis	Glomerular disease as clinical diagnosis
Chahal (2001)[121]	Other (patients with macroscopic haematuria and those older than 50 years with microhaematuria who were evaluated in the haematuria clinic)	Cytology (Centrifuged urine, ≥2 smears obtained)	Features of malignancy were present, e.g. nuclear enlargement, increased nuclear/cytoplasmic ratio, hyperchromasia and irregular nuclear membrane thickness or contour. Features not clearly indicative of malignancy such as papillary clusters were reported as suspicious. Cytology is interpreted as positive if it is suspicious or diagnostic	Final diagnosis (flexible cystoscopy and/or biopsy, IVU and ultrasound)	Any abnormality of the urinary tract

continued

Study details	Participants	Index test	Index test cut-off	Reference standard(s)	Reference standard cut-off
Chisholm (1988)[122]	Other [patients with painless haematuria (without UTI), referred to urology]	DMSA scintigraphy (analogue images were obtained at between 2 and 4 hours after injection of 75 MBq of isotope, using an IGE small field of view gamma camera) IVU (a mild laxative was given the night before the examination. A full-length abdominal radiograph and a tomogram of the renal area were obtained prior to injection of contrast medium. Meglumin/sodium diatrizoate (325 mg iodine/ml) at 1 mg/kg body weight was given intravenously, half before applying abdominal compression and the remainder 3–4 minutes later. Immediately after completion of the injection, 3 renal area tomograms were taken at 1-cm intervals, together with a plain radiograph of the renal area. Compression was then released and a full-length abdominal radiograph obtained, followed by a bladder view after micturition)	Any renal abnormality	Final diagnosis (History, IVU, and DMSA, supplemented as indicated by ultrasound and cystoscopy)	Any renal abnormality

continued

Study details	Participants	Index test	Index test cut-off	Reference standard(s)	Reference standard cut-off
Chong (1999)[123]	Other [patients with painless haematuria (without UTI), referred to urology]	Bard (Covington, USA) BTA tumour marker Cytology	Not reported	Final diagnosis (IVU, flexible cystoscopy, urine cytology, and BTA)	Malignant outcome
Chu, (1990)[81]	Other (patients with 'dipstick haematuria' and established clinical diagnosis)	Nikon (Japan) differential interference microscopy (uncentrifuged urine sample. 100 RBCs observed) Nikon PCM (uncentrifuged urine sample. 100 RBCs observed) Nikon Wright's stain used (centrifuged urine sample, examined by light microscopy on non-consecutive days)	*Glomerular*: >80% of RBCs distorted with variation in size and shape, and fragmentation. Non-glomerular and mixed are classified as negative *Glomerular*: >20% of RBCs with glomerular morphology. Non-glomerular and mixed classified as negative *Non-glomerular*: >80% of RBCs undistorted and uniform in size and shape. Glomerular and mixed classified as negative *Non-glomerular*: <10% of RBCs with glomerular morphology. Glomerular and mixed classified as negative	Previously established diagnosis	Haematuria of glomerular origin
Costa (1996)[82]	Other (patients with haematuria)	Microscopy (centrifuged urine sample, examined under a conventional light microscope at 400× magnification. 100 RBCs per sample were counted. The examination was repeated on a second aliquot)	*Glomerular*: >1% dysmorphic RBCs *Glomerular*: >10% dysmorphic RBCs *Glomerular*: >20% dysmorphic RBCs *Glomerular*: >30% dysmorphic RBCs *Glomerular*: >40% dysmorphic RBCs *Glomerular*: >50% dysmorphic RBCs *Glomerular*: >60% dysmorphic RBCs *Glomerular*: >70% dysmorphic RBCs *Glomerular*: >80% dysmorphic RBCs *Glomerular*: >90% dysmorphic RBCs	Final diagnosis (clinical-laboratory and/or radiological and/or histological findings)	Haematuria of glomerular origin

continued

Study details	Participants	Index test	Index test cut-off	Reference standard(s)	Reference standard cut-off
Cronan (1982)[124]	Other (consecutive patients with painless haematuria, aged ≥45 years, referred to urology)	Cystosonography (initial 25 patients had real-time US prior to voiding immediately after infusion nephrotomography. The next 75 had oral fluids or fluids via a Foley catheter to distend the bladder maximally prior to cystosonography. All US on commercially available sector-scan units with 3.0- or 3.5-MHz focused transducers)	Bladder lesion	Cystoscopy	Detection of any bladder lesion
de Kermerchou (1993)[83]	Query haematuria [patients with haematuria (>10 RBCs/mm^3)]	PCM [uncentrifuged (if >100 RBCs per mm^3) or centrifuged (if <100 RBCs/mm^3) urine. One investigator counted 100 cells on two separate occasions and the average number of dysmorphic cells was reported. If there was a >20% disparity between the counts, a third count was undertaken]	*Glomerular*: >10 dysmorphic RBCs/mm^3 of urine *Glomerular*: >15 dysmorphic RBCs/mm^3 of urine *Glomerular*: >20 dysmorphic RBCs/mm^3 of urine *Glomerular*: >80 dysmorphic RBCs/mm^3 of urine	Previously established diagnosis (patients' medical records were examined for clinical diagnosis of the cause of haematuria)	Haematuria of nephrological (rather than urological) origin

continued

Study details	Participants	Index test	Index test cut-off	Reference standard(s)	Reference standard cut-off
de Metz (1991)[84]	High risk (e.g. known renal or oncology patients) [Patients with dipstick haematuria (>5 RBCs/hpf), and an established clinical diagnosis]	PCM [centrifuged urine sample, examined at 400× magnification. Minimum of 100 RBCs examined and classified as isomorphic if uniform in shape (biconcave discoid) and size, with intact, regular membranes. Dysmorphic erythrocytes were not uniform in size and shape, and had irregular membranes] Light microscopy, using May–Grunwald–Giemsa stain (centrifuged urine sample. RBCs were classified as dysmorphic or isomorphic depending on their size, shape and hypochromia)	*Glomerular*: ≥80% dysmorphic RBCs. Non-glomerular and mixed are classified as negative. *Non-glomerular*: ≥80% isomorphic RBCs. Glomerular and mixed are classified as negative	Previously established diagnosis (renal haematuria confirmed by renal biopsy. Non-renal haematuria confirmed by urological investigation)	Renal haematuria
De Santo (1987)[85]	Haematuria (patients with recurrent haematuria)	Polyvar PCM, urinary RBC morphology (centrifuged urine sample)	*Glomerular*: >80% dysmorphic RBCs on 2 non-consecutive days. Non-glomerular and mixed are classified as negative *Non-glomerular*: ≥80% uniform RBCs. Glomerular and mixed are classified as negative	Final diagnosis (biopsy, clinical and laboratory evidence for post-streptococcal glomerulonephritis, MSU, urinary calcium excretion, US, IVU, cystoscopy and cytology)	Not reported
Docci (1988)[87]	Haematuria (patients with haematuria and normal creatinine)	Coulter urinary RBC size (centrifuged urine sample. Analysis performed within 30 minutes of collection with a Coulter Counter Model S-Plus modified by the Channelyzer attachment. Standard calibration and Isoton III were used)	Glomerular	Final diagnosis (clinical picture and the results of routine urinalysis, urine microbiology, and appropriate investigations in radiology, cystoscopy and immunohistopathology)	Biopsy-proven glomerular disease

continued

Study details	Participants	Index test	Index test cut-off	Reference standard(s)	Reference standard cut-off
Docci (1990)[86]	Other [patients referred to nephrology for investigation of haematuria (>5 RBCs/hpf), in whom a definite diagnosis was established]	Coulter Electronics (USA) urinary RBC size (centrifuged urine sample, sediment resuspended and diluted to 10 ml with Isoton III. Analysed within 30 minutes of collection with the Coulter Counter Model S-Plus. Each patient analysis was repeated to assess reproducibility)	*Glomerular*: mean cellular volume <70 fl	Final diagnosis	Established glomerular disease
Eardley, (2004)[88]	Microscopic haematuria (patients with microscopic haematuria referred either from general practice or from the department of urology after a urological cause of microscopic haematuria had been excluded)	Microalbuminuria	Urinary albumin excretion of 30–299 mg/24 h was considered microalbuminuria (≥30 mg/24 h was considered normal)	Previously established diagnosis (renal biopsy)	IgA nephropathy was defined as the finding of IgA deposition in mesangium on immunoperoxidase study
Fairley (1982)[89]	Haematuria (patients referred to nephrology for investigation of haematuria)	Olympus PCM (centrifuged urine sample)	*Glomerular*: dysmorphic RBCs present	Final diagnosis (renal biopsy where clinical picture suggested glomerular disease, otherwise cystoscopy and appropriate radiological investigations)	Not reported
Fassett (1982)[90]	Haematuria [patients with haematuria (>3000 RBCs/ml urine)]	Olympus microscope with PC attachment PCM (uncentrifuged urine sample)	*Glomerular bleeding*: >80% urinary red cells distorted. Non-glomerular and mixed are classified as negative *Non-glomerular*: >80% urinary red cells undistorted. Glomerular and mixed are classified as negative	Final diagnosis (radiology, cystoscopy, urine microbiology and immunohistopathology)	Not reported

continued

Study details	Participants	Index test	Index test cut-off	Reference standard(s)	Reference standard cut-off
Fünfstück (1989)[91]	Urological patients with confirmed glomerulo-nephritis or urolithiasis	Erythrocyte morphology, urine sediment analysis	*Glomerular*: >70% dysmorphic RBCs. Non-glomerular and mixed classified as negative *Non-glomerular*: <20% dysmorphic RBCs. Glomerular and mixed classified as negative	Previously established diagnosis	Clinical diagnosis of glomerulonephritis
Fukuzaki (1996)[92]	Other (patients with microscopic or macroscopic haematuria)	PCM (>100 RBCs were examined. RBCs were classified as isomorphic if they were uniform in size and shape with intact membranes and dysmorphic if they were not uniform in size and shape and had irregular membranes). Immunocytochemical staining (centrifuged urine sample. Staining of RBCs to identify cells coated with the Tamm–Horsfall protein, which originates from renal tubuli)	*Glomerular*: >70% of red cells in the sediment were dysmorphic. Non-glomerular and mixed were defined as negative *Non-glomerular*: >70% of red cells were normal. Glomerular and mixed are defined as negative	Final diagnosis (clinical diagnostic evaluation including physical examination, ultrasonography and urinary cytology. Excretory urography, CT, MRI, endoscopic examination or renal biopsy was performed in selected patients)	Diagnosis of a renal disorder
Game (2003)[93]	Query haematuria (patients with isolated asymptomatic microscopic haematuria)	Sysmex SE 9000, TAD Medical Electronics Urinary RBC volume PCM (centrifuged urine sample) (fresh urine sediment sample)	'*Glomerular*' RBC volume distribution curve. Non-glomerular and mixed results are defined as negative. Cut-off values not reported '*Non-glomerular*' RBC volume distribution curve. Glomerular and mixed results are defined as negative. Cut-off values not reported	Final diagnosis [physical examination, urinalysis, biochemical analysis of renal function, PCM, radiological evaluation (i.e. sonography, IVU), endoscopy, cystourethroscopy, urine cytology, nephrological evaluation. Renal biopsy to confirm glomerular disease]	Glomerular diagnosis. Non-glomerular diagnosis

continued

Study details	Participants	Index test	Index test cut-off	Reference standard(s)	Reference standard cut-off
Gerc (1997)[94]	Query haematuria [patients with haematuria (>5 RBCs/hpf)]	PCM (400× magnification. 200 RBCs counted by two independent investigators. Microscopy was undertaken within 60 minutes of urine collection)	*Glomerular*: ≥ 10% of RBCs characterised as being glomerular *Glomerular*: ≥ 20% of RBCs characterised as being glomerular *Glomerular*: ≥ 30% of RBCs characterised as being glomerular	Previously established diagnosis (patients' medical records were examined for clinical diagnosis of the cause of haematuria)	A nephrological (rather than urological) cause of haematuria
Gimbel (1988)[95]	Other [patients with haematuria (>5 RBCs/hpf)]	Urinary RBC size (centrifuged urine sample)	*Glomerular*: ≥ 5.7 μm	Final diagnosis (clinical finding; urine status, urine culture, urine cytology; cytoscopy; urography; sonography of the kidney, bladder, prostate; where necessary CT abdomen or renal biopsy)	Diagnosed glomerular bleeding
Glashan 1980[125]	Haematuria (consecutive patients with haematuria)	Plasma CEA	>40 ng/ml >35 ng/ml in males and >110 ng/ml in females	Final diagnosis (cystoscopy, urine culture, biopsy)	Not reported
Goncalves (1986)[96]	Other (patients with haematuria)	PCM (centrifuged urine sample examined at 600× magnification. At least 100 cells were counted, repeated three times where there was sufficient urine)	*Glomerular*: ≥20% dysmorphic RBCs *Glomerular*: ≥35% dysmorphic RBCs *Glomerular*: ≥50% dysmorphic RBCs *Glomerular*: ≥65% dysmorphic RBCs *Glomerular*: ≥80% dysmorphic RBCs	Final diagnosis (includes histopathology and excretory urography)	Patients were categorised as with having haematuria of glomerular etiology or non-glomerular etiology

continued

Study details	Participants	Index test	Index test cut-off	Reference standard(s)	Reference standard cut-off
Gray Sears (2002)[126]	Patients with asymptomatic microhaematuria (≥3 RBCs/hpf)	CT (no bowel preparation, phase 1: contrast material [5-mm collimated helical acquisition (1.5–1 pitch through adrenal glands and kidneys)]. Abdominal compression, 100 ml non-ionic contrast material via i.v. Phase 2: contrast images of adrenal glands and kidneys 2 min after injecting 5-mm collimation at 1.5–1 pitch. Phase 3: after 5-min delay + removal of abdominal compression, 5-mm collimation cross-sectional ureteral images at 1.6–1 pitch from renal pelvis through bladder) IVU (preceded by bowel preparation. Non-contrast upper and lower kidney, ureter and bladder images and nephrotomograms. 100 ml intravenous ionic or non-ionic contrast material)	Any abnormality	IVP and CT (IVU: non-contrast upper and lower kidney, ureter and bladder images and nephrotomograms. 100 ml intravenous ionic or non-ionic contrast material. Contrast tomograms, 5-min, 10-min and post-void images obtained. CT: phase 1 contrast material [5-mm collimated helical acquisition (1.5–1 pitch through adrenal glands and kidneys)]. Abdominal compression, 100 ml non-ionic contrast material via i.v. Phase 2: contrast images of adrenal glands and kidneys 2 min after injecting 5-mm collimation at 1.5–1 pitch. Phase 3: after 5-min delay + removal of abdominal compression, 5-mm collimation cross-sectional ureteral images at 1.6–1 pitch from renal pelvis through bladder. Oblique, delayed and abdominal pressure-enhanced images as needed, renal scans or non-contrast urolithiasis CT possible)	Detection of any abnormality that can cause haematuria

continued

Study details	Participants	Index test	Index test cut-off	Reference standard(s)	Reference standard cut-off
Hirakawa (1995)[98]	Other (patients with haematuria)	Laser Tec (Yokohama, Japan), confocal reflecting-laser microscopy [centrifuged urine sample, sediment examined without fixation and staining. In case of macrohaematuria, a drop of specimen was directly placed on the slide. Erythrocytes from the sample were shown on a TV screen. Maximum magnification rate is 7200× for 1LM01 (a type of laser microscope) and 6400× for 1LM11 (another type of laser microscope). However, 1440× for 1LM01 and 1280× for 1LM11 or 3600× for 1LM01 and 3200× for 1LM11 are suitable for the observation. 30–50 red cells were observed.]	*Glomerular*: >70% of dysmorphic red cells. Non-glomerular and mixed are classified as normal *Non-glomerular*: >70% of isomorphic (normal) red cells. Glomerular and mixed are classified as negative *Glomerular*: >70% dysmorphic red cells. Non-glomerular and mixed are classified as negative *Non-glomerular*: >70% of normal red cells. Glomerular and mixed are classified as negative	Final diagnosis (examination including abdominal ultrasound)	Glomerular disease Urological disease Nephritis
Hyodo (1995)[101]	Other (patients with haematuria and an established clinical diagnosis)	Lasertec laser microscopy, Hyodo–Iino–Miyagawa method (centrifuged urine sample. 30 RBCs assessed by a single observer)	*Glomerular*: ≥ 80% RBCs classified as showing a glomerular pattern. Non-glomerular and mixed are classified as negative *Non-glomerular*: ≥ 80% RBCs classified as showing a non-glomerular pattern. Glomerular and mixed are classified as negative	Previously established diagnosis (cystoscopy, urinary cytology, plain radiography of KUB, IVP and detailed medical urine examination)	Clinical diagnosis of glomerular disease Clinical diagnosis of urological disease

continued

Study details	Participants	Index test	Index test cut-off	Reference standard(s)	Reference standard cut-off
Hyodo (1997)[99]	Other (patients with haematuria)	Toa Medical Electronics (Kobe, Japan) urinary RBC volume (UF-100 automated urinary flow cytometer)	*Glomerular*: >80% of all RBCs were equal to or smaller than the forward scatter intensity of 126. Non-glomerular and mixed patterns are classified as negative *Non-glomerular*: >80% of all RBCs were equal to or larger than the forward scatter intensity of 84 Glomerular and mixed patterns are classified as negative	Previously established diagnosis (included renal biopsy)	Diagnosis of glomerular disease
Hyodo (1999)[100]	Other [patients with haematuria (≥2 RBCs/hpf, without bacteriuria) and an established clinical diagnosis]	Sysmex (Kobe City, Japan) urinary RBC volume [samples were analysed within 1 hour of collection if possible. Samples that could not be analysed within 1 hour were stored at 4°C until they could be examined (within 6 hours)]	*Glomerular*: ≥80% dysmorphic RBCs. Non-glomerular and mixed are classified as negative. *Glomerular*: ≥80% of RBCs have a forward scatter intensity of ≤126 and <80% of all RBCs have forward scatter intensities of at least 84. Non-glomerular and mixed are classified as negative *Non-glomerular*: ≥80% isomorphic cells. Glomerular and mixed are classified as negative *Non-glomerular*: ≥80% of RBCs have a forward scatter intensity of at least 84 and <80% of all RBCs have forward scatter intensities of ≤126. Glomerular and mixed classified as negative	Previously established diagnosis (glomerular disease: IVP, ultrasound, renal biopsy. Non-glomerular disease: IVP, cystoscopy or histological examination, or were patients with haematuria following transurethral surgery or extracorporeal shock wave lithotripsy)	Glomerular disease
Janssens (1992)[102]	High risk (e.g. known renal or oncology patients) (patients with haematuria and an established clinical diagnosis)	Immunocytochemical staining (staining of RBCs to identify cells coated with the Tamm–Horsfall protein, which orginates from renal tubuli) Urinary RBC morphology	*Glomerular*: ≥ 60% coloured cells *Glomerular*: 30% dysmorphic RBCs *Glomerular*: 40% dysmorphic RBCs *Glomerular*: 50% dysmorphic RBCs *Glomerular*: 60% dysmorphic RBCs *Glomerular*: 70% dysmorphic RBCs	Previously established diagnosis (clinical assessment)	Diagnosis certain to be renal or non-renal based on clinical assessment

continued

Study details	Participants	Index test	Index test cut-off	Reference standard(s)	Reference standard cut-off
Jean (1993)[103]	Other [patients with macroscopic or microscopic haematuria or both (analysed separately)]	Coulter Electronic (Hialeah, FL, USA) urinary RBC volume	*Glomerular*: volume >71 fl	Previously established diagnosis (cytology, clinical examination, urological investigations, renal biopsy)	Diagnosis of glomerular disease
Jung (2002)[127]	Other (patients with haematuria)	IDL Biotech, (Sweden) UBCTM (measurement was carried out using MSU) Urine cytology	>12 μg/l TCC	Final diagnosis [cystoscopy was used to confirm transitional cell carcinoma (TCC) of the bladder]	Diagnosis of TCC
Kim (2002)[128]	Other (patients with painless macroscopic haematuria and normal upper urinary tracts on routine CT scans)	Virtual cystoscopy (multidetector scanning. CT datasets were transferred to a workstation for virtual cystoscopy reconstruction using a volume rendering algorithm. Images were adjusted until normal mucosal surfaces appeared smooth and no noise was seen in the lumen. Two experienced radiologists independently interpreted virtual cystoscopic images and discrepancies were resolved by consensus. When a possible abnormality was discovered, it was fully evaluated from various angles)	Any bladder lesion	Cystoscopy	Detection of any bladder lesion

continued

Study details	Participants	Index test	Index test cut-off	Reference standard(s)	Reference standard cut-off
Kirollos (1997)[129]	Other (patients undergoing cystoscopy for suspected bladder cancer)	Bard (Covington, USA) BTA (measurement was carried out using MSU)	Urine cytology	Cystoscopy (Rigid or fibre-optic cystoscopy)	Detection of urothelial malignancy
Kohler (1991)[104]	Haematuria [patients with haematuria (>8 RBCs/μl urine)]	PCM, urinary RBC morphology (400× magnification used to examine a minimum of ten hpf and 100 erythrocytes. RBCs were classified as discocytes, echinocytes, anulocytes, ghosts, schizocytes, stomatocytes, codocytes, knizocytes and acanthocytes)	*Glomerular*: ≥5% acanthocyturia *Glomerular*: ≥10% acanthocyturia *Glomerular*: ≥2% acanthocyturia	Final diagnosis (clinical diagnosis, proteinuria, radiology including renal ultrasound and IVP, biopsy)	Biopsy-proven glomerulonephritis
Kore (1999)[21]	Other (patients with dipstick haematuria and an established clinical diagnosis)	Microbial Systems (Coventry, UK) urinary RBC volume	*Glomerular*: mean cell size <4.75 μm	Final diagnosis	Clinical diagnosis of glomerular disease
Lang (2002)[131]	Other (patients with recurrent asymptomatic microscopic haematuria, defined as dipstick positive or ≥ 5 RBCs/hpf)	CT (four scan sequences were obtained, before, during and after contrast infusion. All scans were obtained at 320–210 MA and 140–120 kV in inspiration with an acquisition time of 24 s per scan or using a cluster technique of 5 contiguous images per 9-s breath hold with 8 s between clusters)	Any abnormality	Histopathology/urological follow-up (histopathological testing in all cases of neoplasm and urological follow-up in all inflammatory and miscellaneous conditions)	Not reported

continued

Study details	Participants	Index test	Index test cut-off	Reference standard(s)	Reference standard cut-off
Lang (2003)[130]	Other (patients with microscopic haematuria, in whom prior urological work-up and imaging studies had failed to identify a responsible lesion)	CT [multi-phasic spiral CT of the pelvis and bladder with 3-or 5-mm collimation (pre-enhancement, arterial, cortico-medullary, nephrographic and excretory phases)]	Any lesion of the lower urinary tract Lesion of the lower urinary tract (neoplasm) Lesion of the lower urinary tract (inflammatory) Lesion of the lower urinary tract (miscellaneous)	Cytology or urological follow-up	Any lesion of the lower urinary tract Lesion of the lower urinary tract (neoplasm) Lesion of the lower urinary tract (inflammatory) Lesion of the lower urinary tract (miscellaneous)
Lui (1986)[105]	Other (patients with haematuria)	Benzidine dye used (centrifuged urine sample. Sediment stained with a solution containing benzidine hydrochloride and sodium nitroferricyanide. Light microscopy used to count the total and number of dysmorphic RBCs/ml) PCM (centrifuged urine sample. Total and number of dysmorphic RBCs/ml counted)	*Glomerular*: majority of RBCs dysmorphic	Previously established diagnosis	Diagnosis of glomerular disease

continued

Study details	Participants	Index test	Index test cut-off	Reference standard(s)	Reference standard cut-off
Misra (2000)[132]	Other (patients with painless haematuria or TCC of the bladder)	Cytology [bladder washing (lavage cytology) was obtained immediately after voiding using normal saline. After washing 3–4 times the effluent was collected. Effluent was centrifuged and multiple smears were prepared. Smears were stained with Papanicolaou stain and haematoxilin and eosin stain] (Freshly voided urine samples were collected usually 3 hours after the first morning void. Urine was centrifuged and multiple smears were prepared from the sediment. Smears were stained with papanicolaou stain and haematoxilin and eosin stain)	Loose clusters or isolated cells with increased nuclear cytoplasmic ratio with fine to coarse chromatin and prominent nuleoli	Cystoscopy and biopsy (rigid cystoscopy. Tumours were classified according to Friedel's grade. Two to three cold cup biopsies were take for histological confirmation)	Histologically confirmed tumour
Mitty (1974)[133]	Other (patients with cystoscopically demonstrated unilateral upper urinary tract bleeding and negative or non-diagnostic excretory and retrograde urograms)	Angiography [selective renal arteriography (n = 46) or aortography (n = 2). Filming duration = 12 s]	Cause of bleeding established	Clinical and roentgenographic evaluation	Cause of bleeding established

continued

Study details	Participants	Index test	Index test cut-off	Reference standard(s)	Reference standard cut-off
Miyanaga (1999)[134]	Other (patients with microscopic haematuria who had consulted urologists)	Konica Matritech (Tokyo, Japan) NMP22 Urine cytology	12 U/ml. Papanicolou classes IV and V	Final diagnosis (cystoscopy alone or in combination with IVU and/or ultrasound)	Not reported
Miyoshi (2001)[135]	Other [patients with microscopic or macroscopic haematuria)	Konica Matritech (Tokyo, Japan) NMP22 Urine cytology (measurement was carried out using MSU)	12.0 U/ml. Papanicolau classification class IV and V (I, II and III as negative)	Examination (included ultrasound and other tests)	Diagnosis of urothelial TCC
Mohammad (1993)[106]	Other [patients with urinary tract symptoms and haematuria (red blood cells detected by PCM)]	PCM (centrifuged urine sample for microscopic haematuria and uncentrifuged urine sample for macroscopic haematuria examined using an oil immersion lens at 800× magnifcation. Dysmorphic RBCs had irregular outline, membrane protrusions, areas of loss of membrane, irregular deposits of cytoplasmic material around the membrane, and variations in size. Isomorphic RBCs had a smooth or crenated outline)	Glomerular: >20% dysmorphic RBCs	Final diagnosis (clinical history, glomerular disease was confirmed by biopsy)	Histologically confirmed glomerulopathy
Mondal (1992)[136]	Other (patients with haematuria)	Urine cytology (50 ml of fresh MSU was collected from all patients for 3 consecutive days. Urine samples were centrifuged. The sediment was spread on glass slides, air dried and stained by May–Gruenwald and Giemsa method. In cases of gross haematuria, acetic acid was used to lyse RBC)	Bladder tumour. TTCs were categorised as grade I, II or III according to the degree of cellular pleomorphism and hyperchromatism and presence of inflammation and necrosis	Histology	Detection of bladder cancer

continued

Study details	Participants	Index test	Index test cut-off	Reference standard(s)	Reference standard cut-off
Murakami (1990)[137]	Population screening [patients with haematuria (>5 RBCs/hpf)]	Cystoscopy Urine cytology Ultrasound IVU	Highly or moderately significant urological lesion, including malignancy (bladder, prostatic or renal pelvic cancer) or other significant lesion (e.g. urolithiasis, vesicoureteral reflux)	Initial diagnosis (cystoscopy, cytology, ultrasound, IVP and other biochemical and imaging investigations and renal biopsy as indicated)	Detection of any significant urological lesion
Nagy (1985)[107]	Other [patients with haematuria (>4–5 RBCs/hpf) and an established clinical diagnosis]	Zeiss Urinary RBC morphology (centrifuged urine sample examined at 400× magnification)	*Non-glomerular*: sediment contained intact, regularly round RBCs of uniform size. Glomerular and mixed (intact and altered RBCs in equal proportion) are defined as negative *Glomerular*: >70% of RBCs showing abnormalities, being small, irregularly shaped and deformed. Non-glomerular and mixed (intact and altered RBCs in equal proportion) are defined as negative	Previously established diagnosis (glomerular: renal biopsy. Non-glomerular: IVU, coagulation tests, cystoscopy and occasional aortography)	Abnormality that accounts for the haematuria
Naicker (1992)[108]	Other [patients with dipstick haematuria (≥1+) and an established clinical diagnosis]	Leitz Laborlux PCM, urinary RBC morphology (centrifuged and uncentrifuged urine samples were examined within 4 h of collection) Coulter (S-plus II with X–Y recorder) urinary RBC volume (peripheral blood and centrifuged urine samples. For analysable curves a minimum RBC count of 0.02×10^{12}/l was required)	*Glomerular*: >50% of RBCs dysmorphic *Glomerular*: urinary RBC size distribution curve that peaked at a volume less than that of the peripheral RBCs. A mixed pattern was recorded if distinct glomerular and non-glomerular populations were present and the glomerular portion was >2% of the total. Treatment of mixed results is unclear	Previously established diagnosis (glomerular haematuria were confirmed by renal biopsy. No details of the examinations used to confirm urological diagnoses were reported)	Established glomerular cause of haematuria

continued

Study details	Participants	Index test	Index test cut-off	Reference standard(s)	Reference standard cut-off
Obronieka (1998)[109]	Other [patients with haematuria (>5 RBCs/hpf)]	PCM (centrifuged urine sample examined at 400× magnification)	*Glomerular*: >60% dysmorphic RBCs. Non-glomerular and mixed are defined as negative *Non-glomerular*: <20% dysmorphic RBCs. Glomerular and mixed are defined as negative	Final diagnosis (standard urological investigation)	Diagnosis of glomerular disease Diagnosis of urological disease
Oge (2001)[138]	Haematuria (patients with haematuria and highly suspicious for bladder cancer)	Konica Matritech (Tokyo, Japan) NMP22	10 U/ml	Cystoscopy	Not reported
O'Malley, (2003)[139]	Other (outpatients with painless haematuria, 40 years of age or older, referred for IVU)	IVU (100 ml of non-ionic contrast medium. Examination included scout KUB and renal tomogram, post-injection renal tomograms, renal film with compression, immediate KUB post-compression release and post-void KUB and additional films as indicated) CT (performed within 2 h of injection of contrast medium for IVU, no additional contrast medium was given. CT was performed with patients in the supine position using the following parameters: collimation 3 mm, reconstruction interval 2 mm, pitch 2:1, 220 mA, and 120 kVp. Examination extended from the top of the kidneys to the base of the bladder)	Filling defect or stricture in the urinary tract. A filling defect was defined as an abnormal structure that displaced contrast media in the urinary tract. A stricture was defined as a narrowing of the urinary tract with proximal dilation	Final diagnosis (All available imaging and cystoscopy, pathology and surgical results including review of medical records and follow-up telephone calls to referring clinicians. At least 6 months follow-up was completed in all patients)	Any abnormality of the urinary tract

continued

Study details	Participants	Index test	Index test cut-off	Reference standard(s)	Reference standard cut-off
Paoluzzi (1999)[140]	Other (patients with macroscopic or microscopic haematuria, presenting to urology)	Konica Matritech (Tokyo, Japan) NMP22 Urine cytology (measurement was carried out using MSU)	≥ 10 U/ml TCC	Final diagnosis (patients clinically suspected of having TCC of the bladder underwent cystoscopy)	Diagnosis of TCC
Quek (2002)[141]	Other (patients referred to urology with microscopic or macroscopic haematuria, cancer surveillance, vesical irritability, others)	BTA tumour marker Urine cytology	Not reported	IVU and cystoscopy with biopsy	Bladder cancer confirmed by biopsy on cystoscopy
Rath (1991)[110]	Dipstick haematuria [participants with glomerular disease (n = 100 specimens) or lower tract disease (n = 22 specimens). All samples were at least 1+ for blood on dipstick testing]	Bright field microscopy (Uncentrifuged urine sample examined at 450× magnification, within 1 h of collection)	*Glomerular*: >80% dysmorphic RBCs. Non-glomerular and mixed are classified as negative *Non-glomerular*: <20% dysmorphic RBCs. Glomerular and mixed are classified as negative	Previously established diagnosis [renal biopsy (n = 51) clinical diagnosis (n = 48)]	Established diagnosis of glomerular disease
Roth (1991)[111]	Other (10 patients with glomerulonephritis, 20 with non-glomerular haematuria)	PCM (centrifuged urine sample)	*Glomerular*: >40% dysmorphic RBCs	Previously established diagnosis (histology)	Histologically confirmed glomerular disease
Saito (1999)[112]	Haematuria [patients with haematuria (>5 RBCs/hpf) and normal creatinine]	Urinary RBC morphology (centrifuged urine sample examined under a conventional light microscope at 400× magnification)	*Glomerular*: >40% dysmorphic RBCs *Glomerular*: >10% dysmorphic RBCs *Glomerular*: >20% dysmorphic RBCs *Glomerular*: >30% dysmorphic RBCs *Glomerular*: >50% dysmorphic RBCs *Glomerular*: >60% dysmorphic RBCs *Glomerular*: >70% dysmorphic RBCs *Glomerular*: >80% dysmorphic RBCs *Glomerular*: >90% dysmorphic RBCs	Previously established diagnosis [glomerular disease was diagnosed by renal biopsy and/or other clinical findings (e.g. proteinuria, casts in urinary sediment). Non-glomerular disease was diagnosed by X-ray, ultrasound, and/or pathology]	Not reported

continued

Study details	Participants	Index test	Index test cut-off	Reference standard(s)	Reference standard cut-off
Sanchez-Carbayo (2000)[142]	Other (subjects at risk of bladder cancer)	IDL-Biotech (Sollentuna, Sweden) TPS tumour marker (solid-phase, one-step, sandwich enzyme immunosorbent assay. Concentrations of TPS, proportional to the intensity of colour at 450 nm, were calculated from the standard curve) IDL-Biotech TPS/creatinine ratio (concentrations of TPS were calculated from the standard curve and normalised by urinary creatinine)	≥ 279 U/L ≥ 230 U/g creatinine	Cystoscopy	Diagnosis of bladder cancer
Sarosdy (2004)[143]	Haematuria (patients with microscopic or macroscopic haematuria)	UroVysion FISH Urine cytology	Bladder cancer	Cystoscopy and/or biopsy	Detection of bladder cancer
Sayer (1990)[113]	50 patients with glomerular and 50 with non-glomerular disorders	Coulter Counter ZM, 850XL recorder. Urinary RBC volume (centrifuged urine sample diluted with 20 ml of isotonic blood cell diluent)	*Glomerular*: broad, uneven distribution curve reflecting the varying size and shapes of dysmorphic RBCs *Non-glomerular*: sharp, peaked curve representing a uniform, homogeneous population of RBCs indicating non-glomerular diseases classified as negative	Previously established diagnosis (renal biopsy and/or definitive laboratory studies for glomerular pathologies. Non-glomerular disorders diagnosed by appropriate urological evaluation)	Positive for glomerular disease

continued

Study details	Participants	Index test	Index test cut-off	Reference standard(s)	Reference standard cut-off
Shichiri (1988)[114]	Haematuria (patients with a single and definite cause of haematuria)	Coulter + (Toa Medical Electronics) Urinary RBC size (centrifuged urine sample, sediment resuspended in 10 ml of diluent and counted in Coulter Counter S-plus II with Channelyser and X–Y recorder for transcribing distribution curve)	*Glomerular*: standard urinary RBC volume distribution with a peak at lower volume than that of peripheral RBC. Non-glomerular and mixed distributions are classified as negative *Non-glomerular*: standard urinary RBC volume distribution with a peak at a higher volume than that of peripheral RBC. Glomerular and mixed distributions are classified as negative	Final diagnosis [either percutaneous renal biopsy or clinical and radiological data (radiology, cystoscopy and urine culture)]	Not reported
Singbal (1996)[115]	Other [patients with haematuria (>5 RBCs/hpf). 61 adult and 19 paediatric patients]	Nikon PCM Light microscopy Light microscopy, using Wright's stain (centrifuged urine sample, examined at 400× magnification. Minimum of 100 RBCs examined and a percentage of glomerular and non-glomerular cells estimated. Non-glomerular: isomorphic, uniform in size, resembling circulating RBC, red cell 'ghosts' that have lost their haemoglobin often seen. Glomerular: RBCs are of various sizes, microcytes are common, distorted cells with irregular outlines, cells appearing to have extruded small blebs of cytoplasm from the cell membrane, budded and bilobed cells, cells with areas of loss of limiting membrane, granular deposition of phase dense material at intervals around the inner aspect of the cell membrane sometimes associated with coalescence of such membrane deposits, doughnut cells with or without blebs)	*Glomerular*: >20% dysmorphic RBCs	Final diagnosis (clinical, radiological, and laboratory findings)	Acute glomerulonephritis diagnosed according to clinical and laboratory criteria. Other glomerulonephropathies were confirmed by renal biopsy. Diagnosis of glomerular haematuria; diagnoses included minimal change nephrotic syndrome with mild mesangial matrix increase, acute glomerulonephritis, focal prolipherative glomerularnephritis, chronic glomerulonephritis, crescentic glomerulonephritis, mesangioproleferative glomerulonephritis, membranous glomerulonephritis, systemic lupus erytheromatosus

continued

Study details	Participants	Index test	Index test cut-off	Reference standard(s)	Reference standard cut-off
Speelman (1996)[144]	Haematuria [consecutive patients with asymptomatic haematuria (>5 RBCs/hpf)]	Ultrasound (kidney, bladder and prostate transabdominal ultrasound. A Convex sector scanner with a 3.75-mHz transducer was used to obtain sagittal and axial views) IVU [after overnight fasting. 50 ml meglumine iotholamate (420 mg/ml iodine). Post-voiding films at 5 and 10 minutes and others as indicated] Ultrasound and IVU (IVU preparation included laxatives and starvation from midnight prior to 50 ml ionic high osmolar meglumine iotholamate containing 420 mg/ml iodine i.v. as a bolus. Films at 5 and 10 minutes and post-void. Other films as deemed necessary by radiologist. Transabdominal US. Real time convex sector scanner with a 3.75-mHz transducer to obtain sagittal and axial views of kidneys, bladder and prostate)	Upper tract pathology	Final diagnosis (all patients had IVU and US. Other tests included cystoscopy, biopsy, retrograde pyelography and CT. If tests were not conclusive diagnosis was based on urologist's opinion)	Not reported

continued

Study details	Participants	Index test	Index test cut-off	Reference standard(s)	Reference standard cut-off
Spencer (1990)[145]	Other (patients with haematuria referred for intravenous urography)	Ultrasound (transabdominal ultrasound examination of the urinary tract, in the supine position, using a 3.5-MHz sector transducer. The bladder was not filled specifically for the examination)	Any abnormality	Intravenous urography (full-length abdominal radiograph was taken initially with supplementary views when possible. I.v. injection of either meglumine diatrizoate and sodium diatrizoate (325 g iodine/l) iopamidol (300 g/l) when indicated at a dose of 1 ml/kg body weight. Immediately after the injection an upper abdominal radiograph was taken followed by a similar film 5 minutes later. A full-length abdominal radiograph was taken roughly 20 minutes after injection, with a view of the bladder when full. The patient finally underwent postmicturation radiography of the bladder)	Detection of any abnormality

continued

Study details	Participants	Index test	Index test cut-off	Reference standard(s)	Reference standard cut-off
Steurer (1990)[146]	Other (ambulant internal medicine clinic patients)	Ultrasound	Any abnormality of the kidney or urinary tract	IVP [after an abdomen overview image, 80 ml of contrast agent (Uromiro) and 80 ml of 0.9% NaCl solution as short infusion over 5 minutes i.v. administered. Further images after 10 and 20 minutes. If urether stones were suspected, diagonal images were taken. Further images for specific indications, e.g. renal artery stenosis]	Any abnormality of the kidney or urinary tract
Sultana (1996)[147]	Query haematuria (patients with microscopic or macroscopic haematuria)	Urine cytology (urine cytology)	Upper tract calculi, isolated upper tract transitional cell carcinoma, hypernephroma or simple renal cyst (diameter >2 cm)	Final diagnosis (cystoscopy, KUB, US, IVU, radiographs and/or CT)	Detection of urological malignancy
Thomas (1996)[148]	Other (patients with macroscopic or microscopic haematuria attending an open-access haematuria clinic)	BTA Urine cytology	Not reported	Final diagnosis (all patients had urine culture, flexible cystoscopy and IVU)	Histologically proven transition cell tumour

continued

Study details	Participants	Index test	Index test cut-off	Reference standard(s)	Reference standard cut-off
Tomita (1992)[116]	Other [patients with haematuria (>5 RBCs/hpf) and an established clinical diagnosis]	Nikon (Tokyo, Japan) differential interference microscopy [centrifuged urine sample examined and RBCs classified into 10 defined shapes (5 glomerular and 5 non-glomerular). Glomerular morphologies were described as: doughnut-like cells with one or more bulbous projections or vesicles ('blebs'); spherical cells with more than one bleb; doughnut-like cells with irregular surface; yeast-like cells; smaller erythrocytes with or without other deformity. Non-glomerular morphologies were described as: normal biconcave disc; spherical cells with a smooth surface; flat swollen cells with a larger diameter; cells with deeper concavity and a smooth surface (e.g. stomatocytes); flat or spherical cells with multiple projections that were not blebs]	*Glomerular*: ≥15% summed glomerular shapes. *Glomerular*: ≥1% doughnut-like cells with one or more blebs	Previously established diagnosis (glomerular disease was confirmed by biopsy)	Established glomerular disease: diagnoses included IgA nephropathy, lupus nephritis, membrano-proliferative glomerulonephritis, non-IgA mesangial proliferative glomerular nephritis, Henoch–Schoenlein purpura nephritis, membranous nephropathy, endocapillary proliferative glomerularnephritis, and minimal change nephrotic syndrome
Uhl (1995)[117]	Other (patients with haematuria)	Light microscopy	*Glomerular*: ≥30% deformed RBCs	Previously established diagnosis	Positive: clinical diagnosis = glomeral disease. Negative: clinical diagnosis = non-glomeral disease
Wankowicz (1991)[118]	Other [patients with haematuria (>5 RBCs/hpf)]	PCM (centrifuged urine sample examined at 400× magnification)	*Glomerular*: >60% dysmorphic RBCs. Non-glomerular and mixed are classified as negative *Non-glomerular*: ≤20% dysmorphic RBCs. Glomerular and mixed are classified as negative	Previously established diagnosis Final diagnosis (included renal biopsy)	Glomerulonephritis. Other renal and nephrological disorders were classed as negative. Non-glomerular cause of bleeding

continued

Study details	Participants	Index test	Index test cut-off	Reference standard(s)	Reference standard cut-off
Wann (1986)[119]	Haematuria [patients with haematuria (>5 RBCs/hpf))	PCM, urinary RBC morphology (centrifuged urine sample)	*Glomerular*: ≥ 80% dysmorphic RBCs. Non-glomerular defined as negative: ≥ 80% isomorphic RBCs	Final diagnosis (a series of examinations including culture, cytology, IVU, cystoscopy, ultrasound, angiography, and renal biopsy if glomerulonephritis was suspected)	Not reported
Yip (1996)[149]	Haematuria (consecutive patients with painless macroscopic haematuria, either through A&E or clinician referral)	Ultrasound (kidney and bladder transabdominal ultrasound, with a full bladder. A curved 3.5-MHz and linear 5-MHz transducer were used) IVU (films included full-length preliminary, 5 minute, 10 minute with compression, full-length post-compression, filled bladder and post-micturition. These were supplemented, where necessary, by oblique views, additional contrast administration, and other special views)	Imaging detectable lesion (calculi) Imaging detectable lesion (malignancy)	Final diagnosis (cystoscopy, urine cytology, various laboratory tests, and other imaging modalities such as CT and MRI where indicated)	Detection of a lesion (calculi) Detection of a lesion (malignancies)

continued

Study details	Participants	Index test	Index test cut-off	Reference standard(s)	Reference standard cut-off
Yip (1999)[150]	Other (patients presenting with painless macroscopic haematuria)	Ultrasound (the kidneys and the bladder were examined in turn, via the trans-abdominal approach. Care was taken to ensure that the bladder was adequately distended prior to the examination. A curved 3.5-MHz transducer was used, supplemented by a 5.0-MHz transducer to delineate the anterior bladder wall. A recent plain KUB radiograph was made available prior to ultrasonography) IVU (a standard series of films, including full-length preliminary, 5- and 10-minute with compression, filled bladder and post-micturition. These were supplemented where necessary by oblique views, tomography, additional contrast administration and other special views in order to obtain maximum information)	Tumour of the upper tract Tumour of the lower tract	Final diagnosis [cystoscopy and imaging. Other basic investigations consisted of full blood count, serum urea, urine microscopy and culture and urine cytology. Other imaging studies (MR and CT) were performed where indicated]	Diagnosis of a urological tumour of the upper tract Diagnosis of a urological tumour of the lower tract

Appendix 6

Bibliography of studies reporting algorithms for the investigation of haematuria

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Appendix 7

Protocol changes

Inclusion criteria

Very few studies were identified that included only children aged <18 years. In general, these addressed the diagnosis of a different subset of conditions from studies of haematuria in the general population. It was therefore decided to include studies where the age of the participants was unspecified, in addition to studies of adults, and studies that included both children and adults, but to exclude studies that were of children only.

Studies that evaluated tests used to investigate haematuria resulting from blunt abdominal trauma were excluded. The objectives of these studies were inconsistent with the focus of the review, which is the investigation of a finding of haematuria where the cause is unknown.

Studies with fewer than 20 participants were excluded.

Appendix 8

Data extraction of included economic evaluations

Is cytology required for a hematuria evaluation?
Hofland CA, Mariani AJ. *Journal of Urology* 2004;**171**:324–6

This record was compiled by CRD commissioned reviewers according to a set of guidelines developed in collaboration with a group of leading health economists.

Health technology
The use of urine cytology (CPT 88108) to detect urothelial malignancy in the evaluation of patients with asymptomatic microscopic haematuria. The full evaluation included excretory urography (IVP; CPT 74400), cystoscopy (CPT 52000), serum creatinine (CPT 80048) and urine culture. Urine cytology, renal ultrasound, retrograde pyelogram and other tests were performed, as indicated.

Disease
Urological and male genital diseases; neoplasms.

Type of intervention
Diagnosis.

Hypothesis/study question
The AUA Best Practice Policy for Asymptomatic Microscopic Hematuria recommends cytology only in patients with risk factors for TCC. These risk factors are:

- history of smoking, analgesic abuse or cyclophosphamide use
- occupational exposure to chemicals or dyes
- age >40 years
- history of gross haematuria, irritative voiding symptoms, urinary tract infection or pelvic irradiation
- prior urological history.

The aim of this study was to evaluate how often urine cytology yielded supportive or unique information that led to the diagnosis of TCC, the cost of that information and whether it would have been obtained using the current best practice guidelines. The perspective adopted in the economic analysis was that of the third-party payer in the USA (Medicare).

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with one episode of gross haematuria or microscopic haematuria. Haematuria was defined as three RBCs/hpf on two of three properly collected urinalyses.

Setting
The setting was secondary care. The economic study was conducted in Honolulu, HI, USA.

Dates to which data relate
The effectiveness data were from 1976 to 1985. The resource use and cost data related to 2002. The price year was 2002.

Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
The cost data appear to have been calculated retrospectively for the same sample of patients as that included in the effectiveness analysis.

Study sample
The study sample comprised 1000 sequential patients who underwent a standardised haematuria evaluation. The use of power calculations to determine the sample size was not reported. No subgroups were formed since the patients received a suite of tests that were compared for diagnostic yield and, as such, acted as their own controls.

Study design
This was a cohort study that was conducted at a single centre. The cytology samples consisted primarily of voided urine collected during an office visit, but some were barbotaged samples collected during cystoscopy. The samples were prepared according to a standard protocol. 'Atypical cells' and interpretations other than TCC were considered negative. The charts of patients with TCC were reviewed to determine whether urine cytology yielded unique information that led to the diagnosis. The charts of patients with a life-threatening diagnosis were carefully examined to determine which single test was most responsible

for the diagnosis. The length of follow-up was to the point of diagnosis. No patients were lost to follow-up.

Analysis of effectiveness
The form of the analysis was not stated, but the results were based on all patients included in the study. Since all of the patients undertook the evaluation, the issue of comparability was not relevant. The health outcome was the diagnosis of a life-threatening malignancy (TCC). The sensitivity and specificity of urine cytology in the detection of TCC were also calculated.

Effectiveness results
From the sample of 1000 with a haematuria evaluation, 660 (66%) underwent urine cytology. Urine cytology was obtained in 40 of the 71 patients eventually diagnosed with TCC of the bladder or upper tracts.

Urine cytology was positive in 25 (3.8%) of the 660 patients.

There were three false-positive results in patients with cystitis.

False-negative results were found in 18 of the 40 patients with TCC who were tested.

In this cohort, the sensitivity of urine cytology to detect TCC was 55% and the specificity was 99.5%.

In total, 88 patients were diagnosed with a life-threatening condition. For those with TCC, urine cytology, IVP, cystoscopy and serum creatinine directly contributed to the diagnosis.

Clinical conclusions
In this cohort, four patients were identified in whom urine cytology provided information that prompted further evaluation or surveillance and was responsible for the diagnosis of TCC.

Measure of benefits used in the economic analysis
The measures of benefits used in the economic analysis were the cases of life-threatening conditions correctly diagnosed and the tests providing unique diagnostic information. These were obtained directly from the effectiveness results.

Direct costs
Discounting was not conducted, but this was appropriate owing to the short duration of the study (less than 1 year). The costs and the quantities were reported separately. The costs to diagnose a life-threatening condition were determined by multiplying the cost of each test by the number of tests performed. The cost data were derived from the Medicare reimbursement schedule for the state of Hawaii. The cost for unique information was calculated as described earlier, except that the number of each test that provided unique information was used as the divisor. The price year was 2002.

Indirect cost
The indirect costs were not included.

Currency
US dollars ($).

Statistical analysis of cost
The cost data were not treated stochastically since only point estimates were provided.

Sensitivity analysis
No sensitivity analysis was undertaken.

Estimated benefits used in the economic analysis
Urine cytology was performed in 660 patients and was diagnostic for a life-threatening condition in 21 cases (3.3%).

IVP was performed in 966 patients and was diagnostic for a life-threatening condition in 53 cases (5.5%).

Cystoscopy was performed in 956 patients and was diagnostic for a life-threatening condition in 68 cases (7.1%).

Serum creatinine was performed in 931 patients and was diagnostic for a life-threatening condition in two cases (0.2%).

The numbers of tests that provided unique information were four (0.6%) for urine cytology, 16 (1.7%) for IVP, 64 (6.7%) for cystoscopy and two (0.2%) for serum creatinine.

Cost results
The total cost for each test was not provided. In fact, the total cost was $33,467 (660 × $50.71) for urine cytology, $89,836 (966 × $93.02) for IVP, $206,442 (956 × $216.54) for cystoscopy, and $6582 (931 × $7.07) for serum creatinine.

Synthesis of cost and benefits
The costs to diagnose a life-threatening condition were $1521 for urine cytology, $1695 for IVP,

$3044 for cystoscopy and $3291 for serum creatinine.

The costs to provide unique information were $8367 for urine cytology, $5616 for IVP, $3235 for cystoscopy and $3291 for serum creatinine.

Authors' conclusions

Urine cytology is a useful test for adjusting a clinician's index of suspicion for patients undergoing a haematuria evaluation. The cost per life-threatening diagnosis for cytology was slightly less than that for excretory urography (IVP), cystoscopy and serum creatinine. The cost of unique information was slightly higher for cytology, but comparable to the other tests used in the algorithm.

CRD commentary

Selection of comparators

The rationale for the choice of the comparators was clear. Urine cytology was compared with other tests that were included in the diagnostic algorithm for haematuria. This allowed a comparative analysis of its diagnostic value in detecting life-threatening causes of haematuria, particularly TCC.

Validity of estimate of measure of effectiveness

The effectiveness data were derived from a single cohort, which was appropriate for the study question. The patients were followed up to determine the diagnostic yield in terms of detecting TCC and other life-threatening conditions. As such, each patient potentially received all the tests in the algorithm (although only 660 patients received urine cytology owing to their risk profile). The analysis appears to have been handled credibly in order to minimise bias and error in relation to the collection and evaluation of the urine samples. Few details of the clinical and demographic details of the sample were given, although the four cases with TCC detected by urine cytology were described in full in the paper.

Validity of estimate of measure of benefit

The benefit measure was intermediate in nature, considering the diagnosis of a life-threatening condition and unique information for each test. Although this provides a measure of the efficiency of the tests to detect TCC, longer run analyses that include a health outcome would help.

Validity of estimate of costs

The cost data were clearly presented and the unit costs and the quantities were reported separately. The source and price year were also given. However, no statistical or sensitivity analyses were performed, although this may be expected when using reimbursement cost data. It is possible that charges were used to proxy real costs and, if so, this will hinder the generalisability of the cost data to other settings.

Other issues

The authors did not compare their results with those of other studies and did not address the issue of generalisability. However, the authors placed their results in the context of the AUA Best Practice Policy for Asymptomatic Microscopic Hematuria. Their findings suggested that, had these guidelines been adhered to (i.e. urine cytology only undertaken on the high-risk members of the cohort), fewer cytologies would have been performed. In addition, the costs would have decreased, all cases detected in this series would have been included and the cost of unique information would have been lower.

Implications of the study

The findings of this study supported the use of urine cytology on high-risk patients in accordance with the AUA guidelines. All four patients in the present series would have been tested, and unique information would have been provided at a lower cost.

Subject index terms

Subject indexing assigned by National Library of Medicine (NLM)

Adult; Aged; Carcinoma,-Transitional-Cell/co (complications); Carcinoma,-Transitional-Cell/pa (pathology); Hematuria/et (etiology); Hematuria/pa (pathology); Human; Male; Middle-Aged; Urine/cy (cytology); Urologic-Neoplasms/co (complications); Urologic-Neoplasms/pa (pathology).

Country code

USA.

Source of funding

None stated.

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The significance of adult hematuria: 1,000 hematuria evaluations including a risk–benefit and cost-effectiveness analysis
Mariani AJ, Mariani MC, Macchioni C, Stams UK, Hariharan A, Moriera A. *Journal of Urology* 1989;**141**: 350–5

This record was compiled by CRD commissioned reviewers according to a set of guidelines developed in collaboration with a group of leading health economists.

Health technology
The study examined urine dipstick tests (2+ protein) and 24-hour urine analysis (150 mg per day) to detect proteinuria, urinalysis using sediment count microscopy and standard haematuria evaluation using tailored excretory urogram (IVP), serum creatinine, urine culture, urine cytology and cystoscopy. Other studies, such as retrograde pyelography, renal ultrasound, CT, arteriography, selective urine cytology, urine tuberculosis cultures, antistreptolysin O titres, C3 and C4 complement and sickle cell preparation, were performed as indicated.

Disease
Urological diseases and disorders.

Type of intervention
Diagnosis.

Hypothesis/study question
The aim of the study was to investigate the incidence and distribution of adult haematuria and also the medical risk benefit and the cost-effectiveness of an adult haematuria evaluation among different subgroups. Included in the cost-effectiveness analysis was the difference in costs between treating patients early (as a result of the intervention) and treating them late (detected in normal clinical practice through the onset of symptoms of cachexia, pain, uremia or life-threatening haemorrhage). The authors also investigated the degree of haematuria versus the diagnostic yield of the chosen suite of tests. Although not explicitly identified in the paper, the comparator was 'do nothing'. The economic perspective adopted was not stated.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised adult male and female patients with asymptomatic gross or microscopic haematuria, without significant proteinuria. Asymptomatic haematuria was defined as >3 RBCs/hpf on three urinalyses, one urinalysis with more than 100 RBCs/hpf or one episode of gross haematuria in the absence of specifically diagnostic symptoms, such as ureteral colic or cystitis. The population was derived from a multiracial, stable, closed Health Maintenance Organisation (HMO) averaging 123,000 patients during the 8 years of the study.

Setting
The setting was secondary care. The economic study was conducted at the Department of Urology, University of Hawaii John A Burns School of Medicine, Honolulu, Hawaii.

Dates to which data relate
Effectiveness data relate to a period between March 1976 and June 1985. The dates to which resource use data relate were not provided. The price year was not stated.

Source of the effectiveness data
Effectiveness data were derived from a single study.

Link between effectiveness and cost data
Cost data were derived prospectively from the same patient sample as that used in the clinical study.

Single study

Study sample
Power calculations were not reported in the determination of the sample size. The sample comprised 1000 consecutive patients who met the inclusion criteria of the study. Patient age ranged from 18 to 92 years (mean 55 years) stratified into 18–29, 30–39, 40–49, 50–59, 60–69, 70–79 and 80+. Patients undergoing repeat verifying urinalyses were instructed to avoid strenuous physical exercise, sexual intercourse, rectal examination and urological or prostoscopic instrumentation for 48 hours before urine collection.

Study design
This was a prospective cohort study conducted at a single centre. Patients were followed up to the point of diagnosis according to the algorithm used (see Health technology field above). Charts were individually reviewed by the chief investigator and data entered on a study card. Results were results of urinalyses for 6 months before investigation, details of all tests performed, whether they were diagnostic or non-diagnostic and whether there were complications as a result of the tests. The cause of haematuria was classified as life-

threatening, significant requiring treatment, significant requiring observation, insignificant or non-diagnostic. No loss to follow-up was reported. Blinding was not included, nor would it have been relevant. Data were analysed using a PC and database management software.

Analysis of effectiveness

The analysis of effectiveness was based on the entire sample. The primary outcomes of the study were: incidence of haematuria; incidence of life-threatening lesions; haematuria and diagnosis of genitourinary cancer; haematuria evaluation results; incidental findings; life-threatening risk of haematuria evaluation; and degree of haematuria versus diagnostic yield.

Owing to the nature of the study design, comparability of patients was not relevant as they all underwent the investigation.

Incidence of haematuria

The incidence in the general population of the HMO was 0.1%; 18–29 years old = 0.21%, 30–39 = 0.59%, 40–49 = 1%, 50–59 = 2.2%, 60–69 = 2.35%, 70–79 = 2.1% and 80+ = 1.41%.

Incidence of significant lesions

The incidence in the general population of the HMO was 18–29 years old = 0.07%, 30–39 = 0.12%, 40–49 = 0.2%, 50–59 = 0.6%, 60–69 = 1%, 70–79 = 0.9% and 80+ = 0.8%.

Incidence of life-threatening lesions

The incidence in the general population of the HMO was 18–29 years old = 0.001%, 30–39 = 0.04%, 40–49 = 0.04%, 50–59 = 0.2%, 60–69 = 0.3%, 70–79 = 0.29% and 80+ = 0.4%.

Haematuria and diagnosis of genitourinary cancer

Of all renal or urothelial cancers between 1960 and 1987, 68% were evaluated because of gross or microscopic haematuria. Haematuria elicited an evaluation of 37% of renal cancers, 67% of pelvic cancers, 67% of ureteral cancers and 84% of bladder cancers.

Haematuria evaluation results

Some 9.1% of those evaluated had life-threatening lesions, 8.2% had a significant lesion requiring treatment, 14.6% had a significant lesion requiring observation, 56.4% had an insignificant finding and 17.7% had no diagnosis. In 3.4% of patients a lesion was discovered incidentally. The incidence of life-threatening cancers among the whole sample (i.e. not stratified by age) was 1.3% (renal), 0.5% (renal pelvic), 0.5% (ureteral), 6.7% (bladder, with 6.5% for bladder cancer) and 0.1% (uretheral). Results were also given for men and women, stratified by age and degree of haematuria as follows:

- Gross haematuria: men >50 years old = 26.3%; men >40 = 24.7%; men <40 = 13%; all men = 24.4%; women >50 = 25%; women >40 = 20.5%; women<40 = 10%; all women = 17.5%.
- Haematuria: men >50 years old = 15.2%; men >40 = 14.4%; men <40 = 8.8%; all men = 13.6%; women<40 = 3.4%; all women = 4.9%.
- Microscopic haematuria: men >50 years old = 26.3%; men >40 = 24.7%; men <40 = 13%; all men = 24.4%; women >50 = 25%; women >40 = 20.5%; women<40 = 10%; all women = 17.5%

Incidental findings

Of the 3.4% with incidental findings, two (0.2%) had potentially life-threatening conditions.

Life-threatening risk of haematuria evaluation

The life-threatening risk for the 1000 patients was 1.1%. This is broken down as (risk/study) or probability of event:

- renal failure from intravenous contrast studies = 0.008
- instrumentation (sepsis) = 0.001
- radiation risk (age <70 years) = 0.001
- intravenous contrast studies (anaphylaxis) = 0.0003
- arteriography (embolism) = 0.008
- anaesthetic risk = 0.001.

Degree of haematuria versus diagnostic yield

As the degree of haematuria increased, so did the diagnostic yield for life-threatening lesions significantly. No patient with <3 RBCs/hpf 6 months before diagnosis had a life-threatening lesion. However, there was no 'safe limit' as 18.6% of patients with life-threatening lesions had at least one urinalysis with < 3 RBCs/hpf 6 months before diagnosis.

Clinical conclusions

Asymptomatic haematuria, whether gross or microscopic, is a significant finding and warrants evaluation from a risk–benefit point of view. The results provide a breakdown of incidences of haematuria and underlying causes among the general population and age-stratified groups.

Economic analysis

Measure of benefits used in the economic analysis

The benefit measure used in the economic analysis was diagnosis (and survival) of a life-threatening lesion for early versus late detection and treatment.

Direct cost

Discounting was not performed owing to the short period of analysis. The direct costs included were the cost of tests in the algorithm, namely IVP, cystoscopy (office based), cystoscopy (with anaesthesia), urine culture and sensitivity, serum creatinine, urine cytology, retrograde urography, renal ultrasound, renal CT scan, arteriogram, urinalysis and professional visits. The authors also included the average cost of the late diagnosis and treatment of patients with a tumour (with gross haematuria for 2 years before detection) and the average cost of treating similar patients who had presented for diagnosis at the onset of either gross or microscopic haematuria. The sources of these cost data were not provided. For each resource, a unit cost was provided and costs and quantities were reported separately (the number of individual tests carried out was specified from the sample of 1000). The cost of treating side-effects was not included in the analysis. The price year was not stated.

Indirect cost

The authors excluded lost earnings and travel costs in their cost calculations.

Currency

US dollars ($).

Statistical analysis of costs

No statistical analysis of costs was undertaken.

Sensitivity analysis

No sensitivity analysis was undertaken.

Estimated benefits used in the economic analysis

Three tumour registry patients (late detection) were identified who ignored symptoms of gross haematuria before presenting with pain, cachexia or life-threatening haemorrhage from metastatic bladder cancer. Their average survival was 17 months. These cases were compared with three patients who were diagnosed early (two with gross and one with microscopic haematuria) with two cases of localised bladder cancer and one with localised renal adenocarcinoma. These patients survived for a least an average of 17 months although the exact survival time was not provided.

Cost results

The total cost of the haematuria evaluation, based on 1000 patients, was $776,717. The average cost per evaluation was therefore $777.

The unit costs of individual tests were as follows: IVP = $180, cystoscopy (office based) = $117, cystoscopy (with anaesthesia) = $1000, urine culture and sensitivity = $51 if positive and $25 if negative, serum creatinine = $21, urine cytology = $21, retrograde urography = $1200, renal ultrasound = $188, renal CT scan = $652, arteriogram = $1526, urinalysis = $14 and professional visits = $60.

The average cost to treat a patient with bladder cancer (metastatic) diagnosed and treated late was $58,475 (until death). The average cost to diagnose and treat similar patients diagnosed early was $9405 (based on a 17-month period). This was an incremental cost of $48,070.

Synthesis of cost and the benefits

Costs and benefits were not synthesised. The authors stated that haematuria evaluation would be cost-effective if the medical costs of haematuria evaluation, plus the costs of medical care for patients diagnosed early, were less than the cost of diagnosing and treating patients late in the course of the disease. In their series, 77 patients were detected early with gastrourinary lesions. The cost of early versus late treatment (incremental cost) would therefore be ($77 \times \$48{,}970 = \$3{,}770{,}690$). The authors noted that 92% of patients diagnosed with localised genitourinary malignancy were detected while the disease was still localised. The result suggests the intervention is highly cost-effective, as the additional cost is five times the cost of the evaluation for the 1000 patients studied.

Conclusions, commentary and implications

Authors' conclusions

The authors concluded that, for all categories studied, except for women under 40 years old with microscopic haematuria, the risk of haematuria evaluation was less than the incidence of life-threatening lesions discovered as a result of evaluation. Asymptomatic haematuria, whether gross or microscopic, "is a significant finding and warrants evaluation from a risk–benefit and cost–effectiveness standpoint".

CRD commentary

Selection of comparators

The rationale for the choice of comparator, no evaluation, was clear and justified by the authors. Patients would be evaluated as part of normal clinical practice.

Validity of estimate of measure of effectiveness

The effectiveness data were derived from a prospective study which was appropriate for the study question. In terms of determining the incidence of haematuria and underlying causes, the sample and methods appear to be robust, but it should be noted that the effectiveness data for the economic evaluation were based on only three matched pairs of patients for early and late detection of malignancy and may not be reliable. However, the rationale for the approach to determine the clinical effectiveness of the evaluation in the long run, compared with the do nothing option, appears to be sound. The study sample covered a wide range of ages and races, and the results were stratified according to age group and degree of haematuria.

Validity of estimate of measure of benefit

The measure of benefit was derived from the diagnosis of a life-threatening malignancy and the life expectancy of patients with either localised or metastatic cancers, based on early versus late detection, respectively. This was an appropriate measure but, as indicated above, the results were based on three matched pairs and therefore there is some doubt about the validity of these results. The analysis was based on three patients with gross haematuria who did not seek medical assistance before the onset of more severe symptoms, which may not be a commonly occurring scenario.

Validity of estimate of costs

The perspective adopted in the analysis was not explicitly stated but was restricted to direct costs only. For the evaluation of haematuria element of the study the authors provided clear data on resources used and unit costs, and did report quantities. However, for the cost-effectiveness analysis only average treatment and diagnosis costs were given and it is not possible to determine what the cost of an average patient entailed. The economic evaluation would have been strengthened by the use of a synthesised analysis of costs and an outcome measure such as LYs gained or QALYs.

Other issues

The authors made useful comparisons of their findings with those from other similar studies, especially with regard to what is considered to be 'normal' haematuria. Discussions of the factors and practices that limit the reliability of the results are also presented (improper collection of urine specimens, trauma due to instrumentation, improper storage, recent excessive exercise, etc.). The authors also stressed the importance of follow-up of patients without a diagnosis after evaluation – in one follow up study by Carson and colleagues, 16% of patients had significant lesions and 0.005% had bladder cancer.

Implications of the study

The results of this study support the evaluation of haematuria from both clinical and economic points of view. The authors recommend that, for patients with >3 RBCs/hpf on two of three properly collected and performed urinalyses, >100 RBCs/hpf on one urinalysis or one episode of gross haematuria, a full evaluation should be undertaken. The serum creatinine level should be established to screen renal function before obtaining contrast medium studies, and urine culture is obtained to screen for bacteriuria before instrumentation. Before cystoscopy, urine cytology is obtained to adjust the clinical index of suspicion. The standard screening tests are an IVP for the upper urinary tracts and cystourethroscopy for the lower tract. Other tests are obtained to define abnormalities further.

Subject index terms

Subject indexing assigned by NLM

Adult; Age-Factors; Aged; Aged,-80-and-over; Cost-Benefit-analysis; Costs-and-Cost-analysis; Female; Hematuria/ec (economics); Hematuria/et (etiology); Human; Male; Middle-Aged; Risk-Factors; Urologic-Diseases/di (diagnosis).

Country code

USA.

Review funding body

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Copyright comments

Cost-effective evaluation of indeterminate urinary cytology.
Novicki DE, Stern JA, Nemec R, Lidner TK.
Journal of Urology 1998; **160**(3 Part 1):734–6

This record was compiled by CRD commissioned reviewers according to a set of guidelines developed in collaboration with a group of leading health economists.

Health technology
The performance of complete urological evaluations by cystoscopy and excretory urography (IVP) was examined in patients with indeterminate urinary cytology. Alternative methods (e.g. ultrasonography, retrograde pyelography or CT) were used for patients with an allergy to contrast media. Three strategies were considered:

- the evaluation of patients with a history of bladder cancer or presenting with haematuria (strategy 1)
- the evaluation of patients with a history of bladder cancer or presenting with haematuria or a history of smoking (strategy 2)
- the evaluation of all patients with indeterminate urinary cytology (strategy 3).

Disease
Urological and male genital diseases; female genital diseases and pregnancy complications; neoplasms.

Type of intervention
Diagnosis.

Hypothesis/study question
The aim of the study was to assess the cost-effectiveness of the three different strategies (see the section above 'Health technology' above), in terms of complete urological evaluations (or otherwise), for detecting cancers (primarily bladder cancer) in patients with indeterminate urinary cytology. The strategy of evaluating no patients was considered the comparator. The perspective adopted in the economic analysis was that of the third-party payer (Medicare and non-Medicare schedules in the USA).

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with indeterminate urinary cytology who could, potentially, be given a complete urological investigation.

Setting
The setting was a hospital. The economic study was carried out in Arizona, USA.

Dates to which data relate
The effectiveness and resource use data corresponded to patients who had undergone urine cytologies between March 1993 and July 1995. The price year was 1997.

Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
The costing was performed retrospectively on the same patient sample as that used in the effectiveness analysis.

Single study

Study sample
Power calculations were not used to determine the sample size. The sample was derived from a total of 9763 cytologies that were performed at the study institution. Of these, 675 were indeterminate and 389 (83% males) underwent cystoscopy and IVP. The distribution of patients in terms of age was as follows: 25% were less than 66 years, 26% were between 67 and 72 years, 25% were between 73 and 77 years, and 24% were 78 years or older. The total number of patients qualified to be evaluated under strategies 1, 2 and 3 were 227, 330 and 389, respectively. The reasons for cytology were haematuria (28%), symptoms of dysuria, frequency and/or urgency (26%), history of bladder cancer (33%) and screening for high risk of bladder cancer (22%). Some patients had multiple indications for cytology and were counted more than once in these statistics.

Study design
This was a retrospective cohort study that was carried out in a single centre. The duration of follow-up was to the point of diagnosis (or otherwise) of cancer.

Analysis of effectiveness
The principle used in the effectiveness analysis was treatment completers only. The clinical outcome measure was the number of cases of cancers detected. The features of patients associated with bladder cancer were investigated through stepwise multivariate logistic regression.

Effectiveness results
Fifty (22%) cancer cases were detected with strategy 1, 59 (18%) with strategy 2 and 60 with strategy 3.

From the multivariate analysis, the patients' features associated with the detection of new cases of bladder cancer were history of bladder cancer ($p < 0.001$; OR 5.57, 95% CI 2.83 to 10.98) and presentation with haematuria, ($p = 0.001$; OR 3.21, 95% CI 1.57 to 6.57).

Clinical conclusions
Patients with indeterminate urinary cytology who are non-smokers and have neither haematuria nor a history of urothelial cancer are at low risk for malignancy.

Economic analysis

Measure of benefits used in the economic analysis
The measure of benefits was the cases of cancer detected. This was derived directly from the effectiveness results.

Direct costs
The costs were not discounted, which was appropriate since they were incurred in less than 1 year. The quantities were not reported separately from the costs. The cost items were reported separately. The cost analysis covered the costs of cystoscopy and IVP from the perspective of Medicare and non-Medicare payment. The price year was 1997.

Indirect costs
The indirect costs were not considered.

Currency
US dollars ($).

Statistical analysis of costs
No statistical analysis of the costs was conducted.

Sensitivity analysis
No sensitivity analysis was conducted.

Estimated benefits used in the economic analysis
Fifty (22%) cancer cases were detected with strategy 1, 59 (18%) with strategy 2 and 60 with strategy 3.

Cost results
According to the Medicare reimbursement schedule, the total costs were $66,965 for strategy 1, $97,350 for strategy 2 and $114,755 for strategy 3. The corresponding values for non-Medicare patients were $214,742 for strategy 1, $312,180 for strategy 2 and $367,994 for strategy 3.

Synthesis of cost and benefits
The ICER was calculated as the additional cost per additional case detected. The ICER for strategy 1 relative to the strategy of no evaluation was $1339 for Medicare and $4295 for non-Medicare patients. The ICER for strategy 2 relative to strategy 1 was $3376 for Medicare patients and $10,862 for non-Medicare patients. The ICER for strategy 3 relative to strategy 2 was $17,405 for Medicare patients and $55,814 for non-Medicare patients.

Conclusions, commentary and implications

Authors' conclusions
Patients with indeterminate urinary cytology who are non-smokers and have neither haematuria nor a history of urothelial cancer are at low risk for malignancy and do not warrant complete evaluation.

CRD commentary
Selection of comparators
The reason for the choice of the comparator was clear. There is considerable doubt about how to evaluate patients with indeterminate cytology results, and the alternative strategies examined allowed an assessment of each approach in terms of the outcomes and costs. The authors also mentioned bladder tumour antigen markers as an alternative to predicting the presence of bladder cancer, but stated that large-scale studies are required fully to evaluate these. The reader should consider whether these approaches apply to his or her own setting.

Validity of estimate of measure of effectiveness
The study design was appropriate for the question being assessed. The sample of 389 patients with both indeterminate results and a full urological evaluation enabled the outcomes to be assessed. Hence it was possible to determine the most appropriate way to treat them. There were 675 patients with indeterminate cytology at the institution, and it would have been interesting had the authors reported the long-term follow-up data for this group. The retrospective nature of the study design might be associated with a degree of selection bias and, therefore, may affect the validity of the results. However, the authors' approach was logical and appropriate. The

authors stated that the study sample was representative of the population normally treated at their institute.

Validity of estimate of measure of benefit
The measure of benefit, the cases of cancer detected by each approach, was appropriate for the study question.

Validity of estimate of costs
The cost data had some limitations in that only the unit costs were provided and these were related to Medicare reimbursement and non-Medicare schedules. The results are therefore not generalisable outside the USA, as they are based on charges and not on opportunity costs.

Other issues
The authors pointed out the issue of assessor subjectivity and skill in conducting urine cytology, which may explain much of the variation in the test results, in particular the indeterminate results. The authors compared their results with other studies in terms of the number of indeterminate results (4–32%) and emphasised the economic and clinical impact of dealing with non-emphatic results. The issue of generalisability to other settings or countries was not addressed.

Implication of the study
The findings supported the view that indeterminate urinary cytology for those who are non-smokers and who have neither haematuria nor a history of urothelial cancer are at low risk for malignancy and do not warrant complete evaluation. The results from studies of bladder tumour markers as an alternative to urine cytology would help determine whether other more cost-effective tests would help in the treatment of patients with indeterminate cytology.

Subject index terms
Subject indexing assigned by NLM
Aged; Cost-Benefit-Analysis; Cytology/ec (economics); Multivariate-Analysis; Reproducibility-of-Results; Urine/cy (cytology); Female; Human; Male.

Country code
USA.

Review funding body
None stated.

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Copyright comments

URL
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Neural network using combined urine nuclear matrix protein-22, monocyte chemoattractant protein-1 and urinary intercellular adhesion molecule-1 to detect bladder cancer
Parekattil SJ, Fisher HA, Kogan BA. *Journal of Urology* 2003;**169**: 917–20.

This record was compiled by CRD commissioned reviewers according to a set of guidelines developed in collaboration with a group of leading health economists.

Health technology
A neural network for the detection of bladder cancer was examined. The network was based on a combination analysis of three tumour markers, specifically urinary intercellular adhesion molecule-1 (UIAM1), nuclear matrix protein-22 (NMP22) and monocyte chemoattractant protein-1 (MCP1). These were measured in urine using commercially available enzyme-linked immunosorbent assays. An algorithm was created with three sets of cut-off values, modelled to be 100% sensitive for superficial bladder cancer, 100% specific for superficial bladder cancer and 100% specific for muscle invasive cancer.

Disease
Neoplasms; urological and male genital diseases; female genital diseases and pregnancy complications.

Type of intervention
Screening.

Hypothesis/study question
The objective of the study was to evaluate the diagnostic and economic outcomes of implementing the neural network, compared with haematuria and cytology, for the screening of bladder cancer. The hypothesis of the study was that the new algorithm could result in higher sensitivity and specificity values than the two standard approaches. Also, it would avoid unnecessary invasive procedures. The study was conducted from the perspective of the hospital.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients presenting to the urology clinic for cystoscopic evaluation.

Setting
The setting was a hospital. The economic study was carried out at the Division of Urology of the Albany Center in Albany, NY, USA.

Dates to which data relate
The effectiveness and resource use data were gathered from November 1999 to September 2000. The price year was not reported.

Source of effectiveness data
The effectiveness evidence was derived from a single study.

Link between effectiveness and cost data
The costing was performed prospectively on the same sample of patients as that used in the effectiveness study.

Single study

Study sample
Power calculations were conducted on the basis of prior studies. The calculations suggested that a minimum sample size of 108 patients was required to achieve a 99% confidence value ($p = 0.01$). The method of sample selection was not reported. The study sample included 253 patients with a mean age of 62.9 years (range: 18–89 years), of whom 182 were men. The sample was split into two groups: group 1 comprised 98 patients with a history of bladder cancer and group 2 comprised 155 patients undergoing initial cystoscopy. Each group was then randomised into two subgroups with comparable demographics.

Study design
This was a randomised double-blind study, which was carried out in a single centre. The method of randomisation was not reported. The patients were not followed after cystoscopy was performed. No loss to follow-up was reported. The physicians were blinded to the results of the urine test or cystoscopy.

Analysis of effectiveness
It appears that all the patients included in the initial study sample have been taken into account when estimating the effectiveness (i.e. intention-to-treat). The primary health outcomes used in the analysis were the specificity, sensitivity, positive predictive value (PPV) and negative predictive value (NPV). The authors stated that the study groups were comparable at baseline.

Effectiveness results
For haematuria, the sensitivity was 92.6%, the specificity 51.8%, the PPV 18.7% and the NPV 98.3%.

For cytology, the sensitivity was 66.7%, the specificity 81%, the PPV 29.5% and the NPV 95.3%.

For NMP22 alone, the sensitivity was 70.4%, the specificity 45.6%, the PPV 13.4% and the NPV 92.8%.

For MCP1, the sensitivity was 14.8%, the specificity 96.5%, the PPV 33.3% and the NPV 90.5%.

For UIAM1, the sensitivity was 14.8%, the specificity 96.5%, the PPV 33.3% and the NPV 90.5%.

For the cancer-sensitive algorithm, the sensitivity was 100%, the specificity 75.7%, the PPV 32.9% and the NPV 100%.

For the cancer-specific algorithm, the sensitivity was 22.2%, the specificity 100%, the PPV 100% and the NPV 91.5%.

For the muscle invasive algorithm, the sensitivity was 80%, the specificity 100%, the PPV 100% and the NPV 99.6%.

Clinical conclusions
The effectiveness analysis showed that the diagnostic characteristics of the neural network were superior to those observed with the standard approaches.

Economic analysis

Measure of benefits used in the economic analysis
The health outcomes were left disaggregated and no summary benefit measure was used. A cost–consequences analysis was therefore conducted.

Direct costs
Discounting was not relevant since the costs were incurred during a short time. The unit costs were analysed separately from the quantities of

resources used. The health services included in the economic evaluation were cytology (including slide preparation and pathologist reading), office cystoscopy and the combined assay. The cost/resource boundary of the analysis was that of the study hospital. The costs were estimated on the basis of assumptions made by the authors. Resource use was based on the test's hypothesis and results. The price year was not reported.

Indirect costs
The indirect costs were not included.

Currency
US dollars ($).

Statistical analysis of costs
The costs were treated deterministically.

Sensitivity analysis
Sensitivity analyses were not conducted.

Estimated benefits used in the economic analysis
See the section 'Effectiveness results' (p. 241).

Cost results
According to current guidelines, cytology and cystoscopy would both be performed on 178 patients, hence the total costs would be $61,054.

Following the proposed approach, the assay would be performed on 178 patients and cystoscopy only on 65 patients, in which case the total costs would be $36,450.

Synthesis of costs and benefits
Not relevant because a cost–consequences analysis was performed.

Conclusions, commentary and implications

Authors' conclusions
The new approach to screening for bladder cancer was effective in detecting the disease, thus reducing the discomfort of unnecessary invasive procedures in false-positive patients. Cost savings were also observed in comparison with the current cancer screening protocol of haematuria and cytology.

CRD commentary
Selection of comparators
The rationale for the choice of the comparator was clear. Haematuria and cytology were selected as the basic comparator because they represented the standard protocol for the detection of bladder cancer at the authors' institution. The reader should decide whether they represent an appropriate comparator in his or her own setting.

Validity of estimate of measure of effectiveness
The analysis of effectiveness used a double-blind randomised study, which was appropriate for the study question. However, the random allocation procedure was used only to define the algorithm cut-off levels, because the study intervention was then applied to all individuals included in the initial study sample. Thus, the effectiveness study appears to have been based on a within-group comparison since all patients underwent both the standard and the new approaches. It was unclear whether the study sample was representative of the study population since there were few details of either the study sample or the method used to select it. The method of randomisation was not reported. Power calculations were performed in the preliminary phase of the study. Hence, the sample size was appropriate for the study question. These issues tend to enhance the internal validity of the effectiveness study.

Validity of estimate of measure of benefit
No summary benefit measure was used in the economic analysis. The analysis was therefore categorised as a cost–consequences analysis.

Validity of estimate of costs
The economic analysis was conducted from the perspective of the hospital. Only those costs strictly related to the performance of the tests were included in the analysis. The unit costs and the quantities of resources used were reported separately, thus simplifying the reproducibility of the study in other settings. The costs were treated deterministically and no sensitivity analyses were conducted. Thus, the cost estimates were specific to the study setting. The cost data were derived from assumptions made by the authors. The adoption of a wider perspective and the subsequent inclusion of more cost items would have been helpful. The price year was not provided.

Other issues
The authors made some comparisons of their findings with those from other studies. However, they did not address the issue of the generalisability of the study to other settings. Sensitivity analyses were not performed, hence the external validity of the analysis was low. The authors stated that their model may not be applicable to all clinical settings because of the procedures and speed required to analyse the specimens.

Implications of the study
The study results suggested that tumour markers might be useful in detecting bladder cancer and in avoiding unnecessary invasive procedure in patients with no cancer, thus having important implications for the patients' quality of life. The authors noted that their new approach might be useful for monitoring patients with a history of bladder cancer, by modifying the sensitivity and specificity of the screening test on the basis of cut-off levels.

Subject index terms
Subject indexing assigned by NLM
Adolescent; Adult; Aged; Aged,-80-and-over; Bladder-Neoplasms/di (diagnosis); Bladder-Neoplasms/pa (pathology); Carcinoma,-Transitional-Cell/di (diagnosis); Carcinoma,-Transitional-Cell/pa (pathology); Double-Blind-Method; Enzyme-Linked-Immunosorbent-Assay; Female; Hematuria; Human; Intercellular-Adhesion-Molecule-1/ur (urine); Male; Middle-Age; Monocyte-Chemoattractant-Protein-1/ur (urine); Neural-Networks-(Computer); Nuclear-Proteins/ur (urine); Predictive-Value-of-Tests; Sensitivity-and-Specificity; Tumor-Markers,-Biological/ur (urine)

Country code
USA.

Review funding body
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Copyright comments
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URL
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Urinary tract cancer screening through analysis of urinary red blood cell volume distribution. Wakui M, Shiigai T. *International Journal of Urology* 2000;**7**:248–53.

This record was compiled by CRD commissioned reviewers according to a set of guidelines developed in collaboration with a group of leading health economists.

Health technology
Urinary tract cancer screening through analysis of urinary RDC curves compared with conventional screening, which evaluates all patients with microhematuria for urological disorders.

Disease
Neoplasms.

Type of intervention
Screening.

Hypothesis/study question
What is the cost-effectiveness of mass screening for urinary tract cancer using RDC compared with conventional screening? The comparator was justified as the procedure that patients would normally undergo. The perspective was that of a third-party payer, the Japanese Health Insurance System (JHIS).

Economic study type
Cost-effectiveness analysis.

Study population
The study population was males and females aged between 20 and 79 years who had a positive urine dipstick test indicating the presence of occult hematuria.

Setting
The study was set in Japan, in five secondary care hospitals. The economic study was performed retrospectively on the patients within this Japanese setting.

Dates to which data relate
The identification of patients with positive dipstick results was undertaken from 1989 to 1990. Although not explicitly stated, it was implicit that the RDC screening was performed at the time of positive identification.

The year of resource use was presumed to be the same as the year when the effectiveness data was gathered. The price year was not stated.

Source of effectiveness data
Evidence for final outcomes was derived from a single study.

Link between effectiveness and cost data
Costing was undertaken on the same patient sample as that used in the effectiveness study. Data on the resources used during screening were collected prospectively.

Single study

Study sample
A total of 21,307 adults participating in a health screening programme at the hospital were

enrolled. Patients were excluded if they did not have a positive dipstick test over +1 (which would indicate the presence of occult haematuria), had gross haematuria, diagnosed urological diseases, were undergoing treatment or were women during their menstrual period. It is not stated how the initial population was selected for the health screening programme. The sample size was not designed to assure a particular power.

A total of 912 adults were eligible for the study and had an RDC test. This study population was appropriate, as they would normally have undergone further tests if they had asymptomatic microhaematuria. Five of the 912 patients were unable to provide a detailed enough RDC result and were excluded. Thirty-eight of the 907 were classified as high risk (Group 1), defined as having a normocytic or mixed pattern result, and underwent a full urological examination (standard conventional screening); 869 were low risk (Group 2), defined as having a microcytic pattern result, and underwent no further tests.

Study design
This was a five-site, multi-centre study. The design of the study was a non-randomised, prospective study. Patients were followed up for 3 years from the RDC test. No patients in Group 1 and 4.1% in group 2 were lost to follow-up.

Analysis of effectiveness
Intention-to-treat analysis was carried out on all patients who were not lost to follow-up.

The primary health outcomes used in the analysis were as follows:

- number of urological malignancies detected
- number of gross haematurias detected
- number with microhaematuria
- number of Group 2 patients who reported they were alive and well and without serious disease at the follow up point at 3 years.

The comparability of groups at baseline was not assessed.

Effectiveness result
On further examination of Group 1, 52.6% had no abnormal findings, 39.5% had benign disease and 2.6% had bladder cancer.

For Group 2, 95.6% reported that they were alive and well at the 3 year follow-up. Of these, 1.7% had had gross haematuria, which was subsequently diagnosed as either simple cystitis or urolithiasis; 0.2% of Group 2 patients had died from non-urological-related reasons.

Clinical conclusions
Patients requiring a complete urological evaluation could be safely selected on the basis of urinary RDC from the general population who have asymptomatic microhaematuria. Normocytic or mixed patterns from RDC tests led to 43% of this group having a diagnosed urological problem.

Economic analysis

Measure of benefits used in the economic analysis
The authors concluded that the RDC test was sufficient to identify safely and effectively those patients who needed further examination and those who did not. Consequently, a cost-minimisation analysis was performed.

Direct cost
All the costs of tests were assumed to occur in year one. The costs of any urological-related treatments other than screening were not included. Discounting was not performed.

The authors assumed that each patient received one of each appropriate test. The RDC test also included the cost of a urinalysis. Group 1 patients also received a urine cytology, blood count, blood biochemistry, ultrasound sonography, drip infusion urography and a cystoscopy. The authors reported that the costs did not include consultant fees.

Unit prices, taken from the approved rates given by the JHIS, were given for each test. The RDC cost is not yet approved by the JHIS.

The cost perspective was the cost to the JHIS of screening and diagnosing patients.

The year for price data and any possible inflation rates used were not stated.

Indirect costs
Indirect costs were not included in the analysis.

Currency
Japanese yen (Y). No conversions were undertaken.

Sensitivity analysis
A sensitivity analysis was not undertaken.

Estimated benefits used in the economic analysis
The reader is referred to the effectiveness results reported above.

Cost results
By only doing a full urological examination on those patients identified as high risk in the RDC test, a saving of Y40,790,860 for 907 patients was achieved. This represented an average saving of Y44,973 per patient.

Synthesis of cost and benefits
A synthesis of costs and benefits was not relevant as a cost-minimisation analysis was undertaken.

Conclusions, commentary and implications

Authors' conclusions
Compared with conventional screening, the RDC method is both safe and cost saving. A complete urological work-up is only necessary for the small group of patients with normocytic or mixed haematuria RDC results.

CRD commentary
Selection of comparators
The RDC test prevents patients undergoing a full urological examination. The tests involved in this full examination are reported earlier in this abstract and were assumed to occur if the RDC test was not performed. The user of the database should decide if this particular patient group would normally undergo such tests in their own setting.

Validity of estimate of measure of effectiveness
This non-randomised study had a study sample taken from a large sample of patients undergoing health screening. The paper did not report how these people were initially selected, although it seems they were part of a mass health screening programme. If mass screening of this nature is not current practice in the reader's own setting, he or she must consider how they would select people for RDC testing. Patients were not randomly selected and it is unclear how they were selected into the mass screening programme initially. Consequently, the sample in this study may be biased and this should be taken into account when interpreting the effectiveness and cost results.

Validity of estimate of measure of benefit
The analysis of benefits was based upon the therapeutic equivalence of treatment (screening) alternatives. Consequently, the economic analysis only included costs. Therapeutic equivalence was defined as not undergoing urological treatment for microhaematuria during the past 3 years and being alive and well without serious illness at the 3-year follow-up point. If the reader expects that a full urological examination would detect problems not covered by these two definitions of therapeutic benefit, the benefits of RDC testing would be reduced.

Validity of estimate of costs
The implicit perspective of the JHIS included direct costs. However, these costs were only for screening and excluded the cost of treatment of those patients requiring it during the follow-up period. It is likely that this would not adversely affect the overall result of the study, particularly if a full examination would have led to the same treatment experienced by those patients just receiving an RDC test. In other words, such costs would be common to both treatment (screening) arms. The reader should decide if this is the case in his or her own setting. Implicit in the paper is that patients receive one of each appropriate test dependent upon their risk categorisation. Consequently, quantities and costs were reported separately.

No statistical analysis of quantities of resources was performed, although this would seem reasonable given that each patient only receives one of each test.

Prices were taken from a published source, and represented the rates approved by the JHIS. The price year was not stated and a sensitivity analysis of prices was not conducted. No discounting was performed as all costs were incurred in year one. If costs incurred in other years, such as treatment costs, were to be included, then discounting should be taken into consideration.

Other issues
The authors made appropriate comparisons of their findings with those from other studies. Although they did not explicitly address the generalisability of the results, they did conclude that the RDC screening test was both safe and cost saving.

The authors' conclusions answer the study question and they have presented their results in a non-selective manner. They reported the strengths of the RDC test but did not comment on the limitations of the study itself. In particular, there

was no discussion of the accuracy of selecting people identified as having a positive urine dipstick test result, the specificity and sensitivity of both this urine test and the RDC. The cost of detecting urological problems using the RDC test presented in this study is therefore relevant only for those patients who have had a positive dipstick test.

The reader should decide if the 3-year time span in this study is appropriate to his or her own setting. If follow-up screening would normally occur within 3 years, the results are more generalisable. If, however, screening should occur after 3 years, the authors offer no evidence or conclusions on the accuracy of the RDC test after 3 years.

Implications of the study
The authors concluded that RDC is safe and cost saving for screening patients with asymptomatic microhaematuria when compared against conventional, full screening practice. Consequently, they argue that complete urological work-up for asymptomatic microhaematuria should be restricted to those patients with normocytic or mixed haematuria, as identified by the RDC. Those identified with microcytic haematuria are safe from urological cancer.

Subject index terms
Subject indexing assigned by NLM
Adult; Aged; Blood-Cell-Count; Female; Follow-Up-Studies; Hematuria/et (etiology); Human; Male; Mass-Screening/mt (methods); Middle-Age; Urine/cy (cytology); Urologic-Neoplasms/bl (blood); Urologic-Neoplasms/co (complications).

Country code
Japan.

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None stated.

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Copyright comments

URL
http://nhscrd.york.ac.uk/online/nhseed/20001090.htm

NMP22 is a sensitive, cost-effective test in patients at risk for bladder cancer
Zippe C, Pandrangi L, Agarwal A. *Journal of Urology* 1999;**161**:62–5

This record was compiled by CRD commissioned reviewers according to a set of guidelines developed in collaboration with a group of leading health economists.

Health technology
This study evaluated the use of an enzyme immunoassay for nuclear mitotic apparatus protein in voided urine (NMP22) as a marker for the early detection of TCC of the bladder in patients with haematuria or other indications at risk for malignancy. The sensitivity and specificity of NMP22 were compared with those of urinary cytology.

Disease
Neoplasms; urological and male genital diseases.

Type of intervention
Screening; diagnosis.

Hypothesis/study question
The aim of the study was to determine the clinical use of NMP22 as a urinary marker for the early detection of TCC of the bladder in patients with haematuria or other indications at risk for malignancy. The authors compared the sensitivity and the specificity of the NMP22 test with those of urinary cytology. To ensure the validity of the tests, the results of both tests were compared with cystoscopic findings. The authors also wished to assess whether NMP22 was associated with a cost advantage over urinary cytology. Urinary cytology was explicitly regarded as the comparator, as it represented current practice in the authors' setting. The study perspective was not reported. The authors only included the costs of the tests and subsequent cystoscopy for positive test results, implying a hospital/health insurance perspective.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with microscopic or gross haematuria or other indications for risk of bladder cancer.

Setting
The setting was secondary care. The economic study was carried out in Cleveland, OH, USA.

Dates to which data relate
The effectiveness data were collected between April 1997 and February 1998. The dates for the resource use data were not reported. The price year was not reported.

Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
Cost data were collected from reimbursement and charge data in the authors' institution.

Single study

Study sample
No power calculations were reported to determine the sample size. All patients who were referred to the urology clinic for microscopic or gross haematuria or other indications for risk of bladder cancer were asked to provide a urine sample. The samples from 330 patients were tested by both the NMP22 and urology cytology tests, and all of the 330 patients were included in the final analysis.

Study design
The study was a single-centred, controlled trial carried out in the Cleveland Clinic Foundation. All patients were asked to provide a urine sample for the NMP22 test and cytology before cystoscopy. The urine was collected and divided into two aliquots, one of which was transported to the urology laboratory for NMP22 analysis and the other to the cytopathology laboratory of the Cleveland Clinic. The urologist and pathologist were masked to the results of the test. The follow-up was limited to cystoscopy for all patients. The authors did not report the period between the patients providing samples for the tests and cystoscopy. There was no loss to follow-up.

Analysis of effectiveness
All patients included in the study were accounted for in the analysis. The primary outcome measures were the sensitivity, specificity, PPV and NPV of both the NMP22 test and the cytology test.

Effectiveness results
The sensitivity of NMP22 test was 100% (18/18 true-positive tests for bladder cancer) (95% CI: 82 to 100). The sensitivity of the cytology test was 33% (6/18 true-positive tests for bladder cancer) (95% CI: 13 to 59).

The specificity of the NMP22 test was 85% (267/312 true-negative tests for bladder cancer) (95% CI: 82 to 90), whilst the specificity of the cytology test was 100% (312/312 true-negative tests for bladder cancer) (95% CI: 97 to 100).

The PPV of the NMP22 test was 29% (18 true-positive tests out of 63 positive tests) (95% CI: 18 to 63), in contrast to the cytology test, for which the PPV was 100% (6/6) (95% CI: 54 to 100).

The NPV of the NMP22 test was 100% (266/266) (95% CI: 99 to 100) and that of the cytology test was 96% (312 true-negative tests out of 324 negative tests) (95% CI: 94 to 98).

Clinical conclusions
The authors concluded that urinary NMP22 is an effective, simple and non-invasive marker for the detection of bladder cancer.

Economic analysis

Measure of benefits used in the economic analysis
No summary measure of health benefit was defined in the economic analysis. This was therefore a cost–consequences analysis.

Direct costs
Costs and quantities were not reported separately. The costs for the hospital were based on the charges and reimbursement levels, rather than prices, for the tests at the institution at which the study was undertaken (Cleveland Clinic Foundation). The following direct costs were included in the analysis: the charge for an NMP22 test ($20 per sample); the charge for a urinary cytology test ($100); the reimbursement cost for each cystoscopy ($106 for Medicare and $416 for private insurance carriers). Discounting was not required owing to the implicit short time frame of the study. The price year was not reported.

Indirect costs
No indirect costs were included in the analysis.

Currency
US dollars ($). No currency conversions were reported.

Statistical analysis of cost
No statistical analysis of costs was conducted.

Sensitivity analysis
No detailed sensitivity analysis was reported, but the authors did explore the impact of the type of

reimbursement schedule (Medicare versus private insurance carrier) on costs.

Estimated benefits used in the economic analysis

The reader is referred to the effectiveness results reported earlier.

Cost results

The authors reported that elimination of 267 cystoscopies through the use of urinary NMP22 would result in a cost saving ranging from $28,032 to $111,072 (depending on the type of insurance carrier). For the 330 patients requiring evaluation, the authors reported that the cost of NMP22 testing would be $6600, compared with $33,000 for cytology testing, thus producing an overall cost saving of $26,400. The use of the urinary NMP22 test versus urinary cytology to determine whether cystoscopy is required to eliminate the risk of bladder cancer would result in a cost saving of $54,072–137,472 and a saving of at least $3039 per diagnosis of bladder cancer.

Synthesis of costs and benefits

No synthesis of costs and benefits was reported.

Conclusions, commentary and implications

Authors' conclusions

The authors concluded that urinary NMP22 is a simple, non-invasive, cost-effective marker for the detection of bladder cancer.

CRD commentary

Selection of comparators

A justification was given for the choice of comparator used, namely that it represented current practice in the authors' setting. The reader, as a user of this database, should decide if this is a widely used health technology in his or her own setting.

Validity of estimate of measure of effectiveness

The analysis was based on a controlled trial design. Urine samples from each patient were divided into two and tested using both of the screening tests. The results for each test were compared with cystoscopy plus biopsy (the gold standard diagnosis tool) to determine the sensitivity and specificity of each. This design was appropriate for the study question. The urologist and pathologist who compared the screening test results with the cystoscopy and biopsy data were masked to the test used to obtain the screening data. The study sample appears to have been representative of the study population. However, the authors did not report the methods used to select patients for participation in the trial, or whether all relevant patients were included. The authors did not report details of the patients excluded from the trial or who refused to participate. The authors did not report the sample size required to detect statistically significant differences. Appropriate statistical analyses were undertaken to take account of potential biases.

Validity of estimate of measure of benefit

The authors did not derive a summary measure of health benefit, hence there was no measure of the impact on health status of differences in sensitivity and specificity between the tests. The tests had different profiles in terms of false-positive and false-negative results. It is important to assess the impact of these differences on the health and social well-being of patients.

Validity of estimate of costs

The only costs reported by the authors were the cost per sample of the NMP22 test and urinary cytology and the reimbursement cost of each cystoscopy procedure following a positive screen test result. Costs and quantities were not reported separately. The study used charges rather than unit costs in the cost estimates. Charges do not reflect opportunity cost and the use of charges, without also reporting resource use data, limits the generalisability of the study's findings. The authors did not report any currency conversions and discounting was not undertaken because of the short time frame of the study.

Other issues

The authors made appropriate comparisons of their findings with those from other studies, but did not fully address the issue of generalisability to other settings. The study enrolled patients with symptoms of microscopic gross haematuria and other indications for risk of bladder cancer, and this was reflected in the authors' conclusions. The authors did not, however, report any limitations to their study.

Implications of the study

The authors concluded that urinary NMP22 is a simple, non-invasive, cost-effective tumour marker for the detection of bladder cancer. Consequently, they proposed that the use of NMP22 might replace urinary cytology and reduce the frequency of diagnostic cystoscopy in the future.

Subject index terms

Subject indexing assigned by NLM

Aged; Cost-Benefit-Analysis; Middle-Age; Nuclear-Proteins/ec (economics); Predictive-Value-of-Tests; Risk-Factors; ROC-Curve; Sensitivity-and-Specificity; Tumour-Markers,-Biological/ec (economics); Bladder-Neoplasms/di (diagnosis); Bladder-Neoplasms/ur (urine); Nuclear-Proteins/ur (urine); Tumour-Markers,-Biological/ur (urine); Comparative-Study; Female; Human; Male.

Country code

USA.

Review funding body

None stated.

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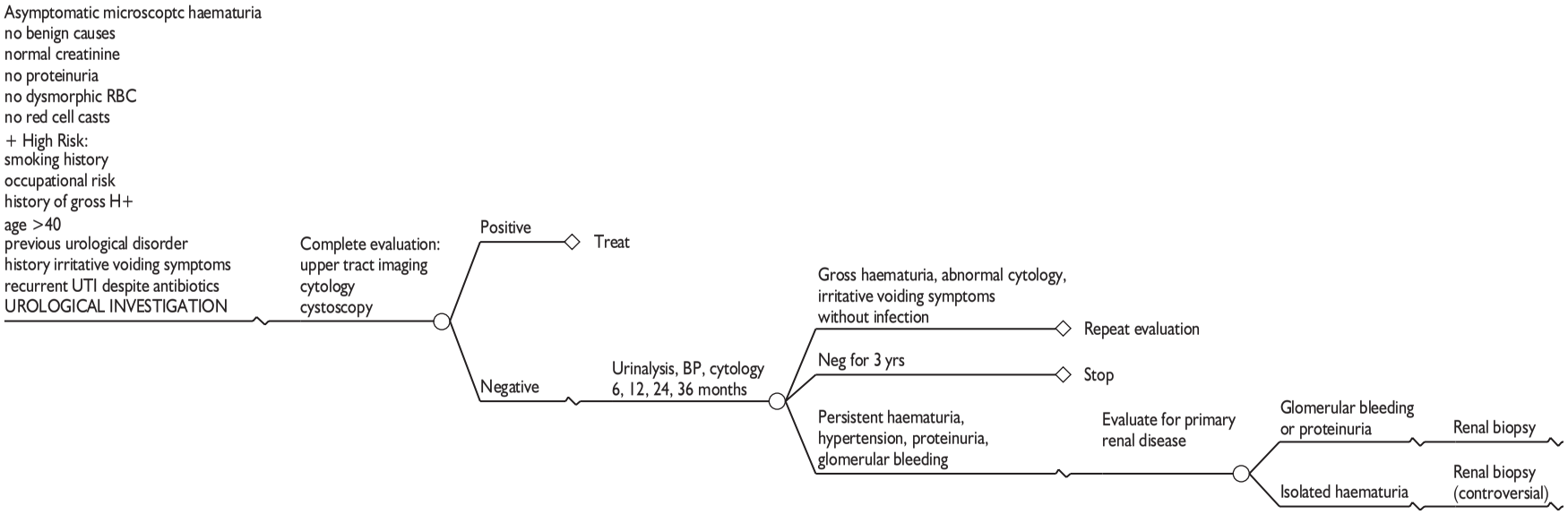
URL

http://nhscrd.york.ac.uk/online/nhseed/19990056.htm

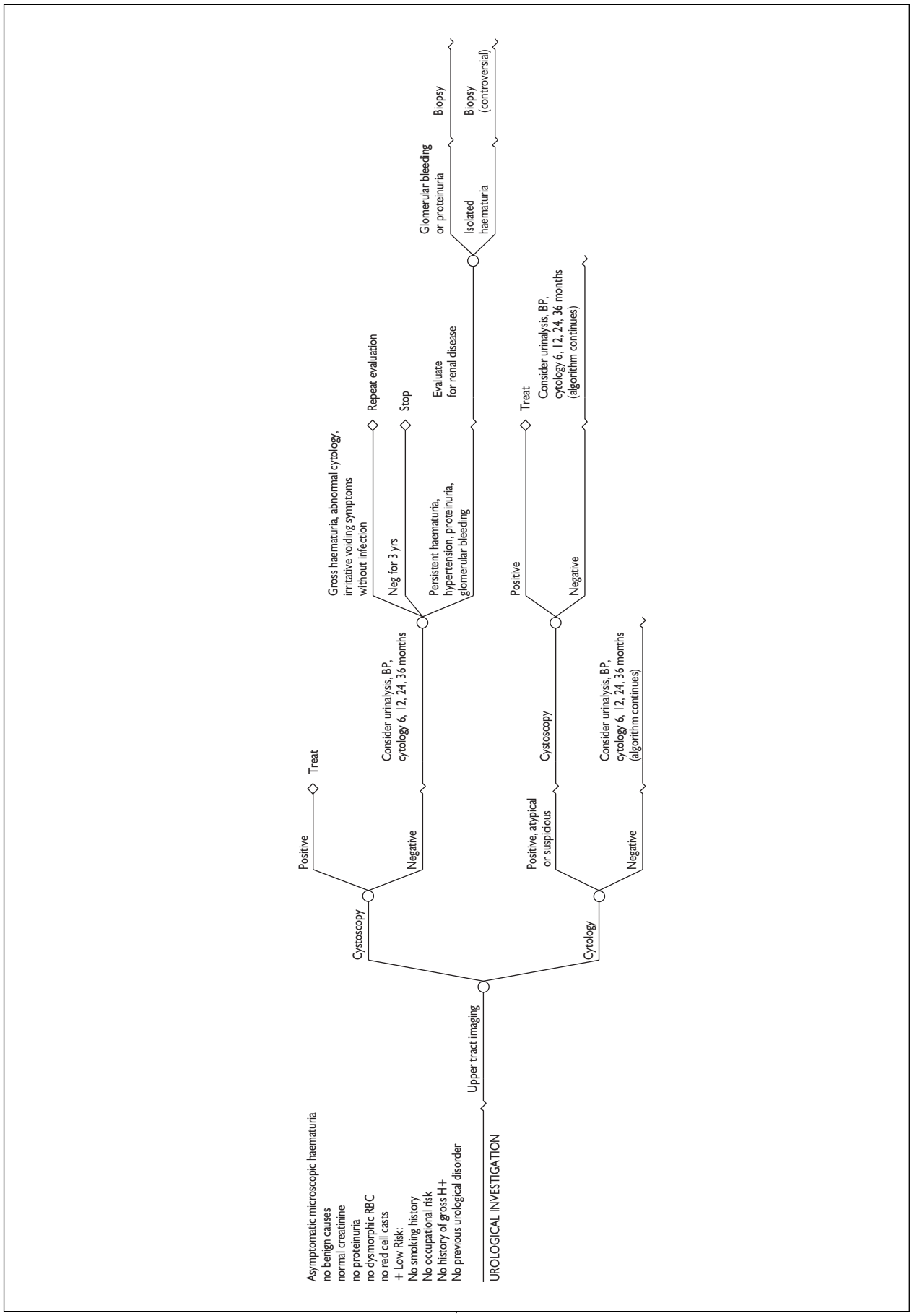
Appendix 9

AUA best practice guidelines for urology (high-risk patients)


Asymptomatic microscoptc haematuria
no benign causes
normal creatinine
no proteinuria
no dysmorphic RBC
no red cell casts
+ High Risk:
smoking history
occupational risk
history of gross H+
age >40
previous urological disorder
history irritative voiding symptoms
recurrent UTI despite antibiotics
UROLOGICAL INVESTIGATION
Complete evaluation:
upper tract imaging
cytology
cystoscopy
Positive
Treat
Negative
Urinalysis, BP, cytology
6, 12, 24, 36 months
Gross haematuria, abnormal cytology,
irritative voiding symptoms
without infection
Repeat evaluation
Neg for 3 yrs
Stop
Persistent haematuria,
hypertension, proteinuria,
glomerular bleeding
Evaluate for primary
renal disease
Glomerular bleeding
or proteinuria
Renal biopsy
Isolated haematuria
Renal biopsy
(controversial)

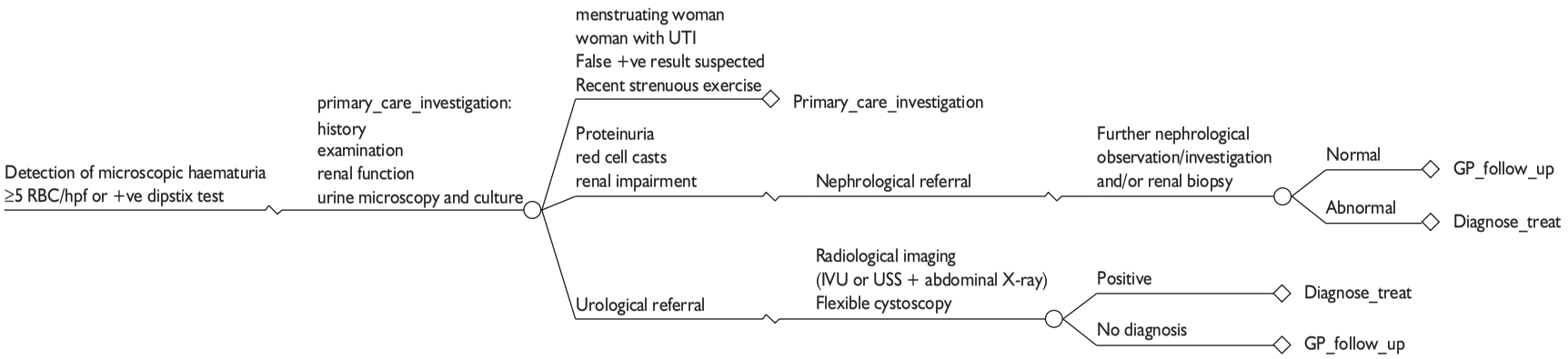
Appendix 10

AUA best practice guidelines for urology (low-risk patients)


Asymptomatic microscopic haematuria
no benign causes
normal creatinine
no proteinuria
no dysmorphic RBC
no red cell casts
+ Low Risk:
No smoking history
No occupational risk
No history of gross H+
No previous urological disorder
UROLOGICAL INVESTIGATION
Upper tract imaging
Cystoscopy
Positive
Treat
Negative
Consider urinalysis, BP, cytology 6, 12, 24, 36 months
Gross haematuria, abnormal cytology, irritative voiding symptoms without infection
Repeat evaluation
Neg for 3 yrs
Stop
Persistent haematuria, hypertension, proteinuria, glomerular bleeding
Evaluate for renal disease
Glomerular bleeding or proteinuria
Biopsy
Isolated haematuria
Biopsy (controversial)
Cytology
Positive, atypical or suspicious
Cystoscopy
Positive
Treat
Negative
Consider urinalysis, BP, cytology 6, 12, 24, 36 months (algorithm continues)
Negative
Consider urinalysis, BP, cytology 6, 12, 24, 36 months (algorithm continues)

Appendix 11

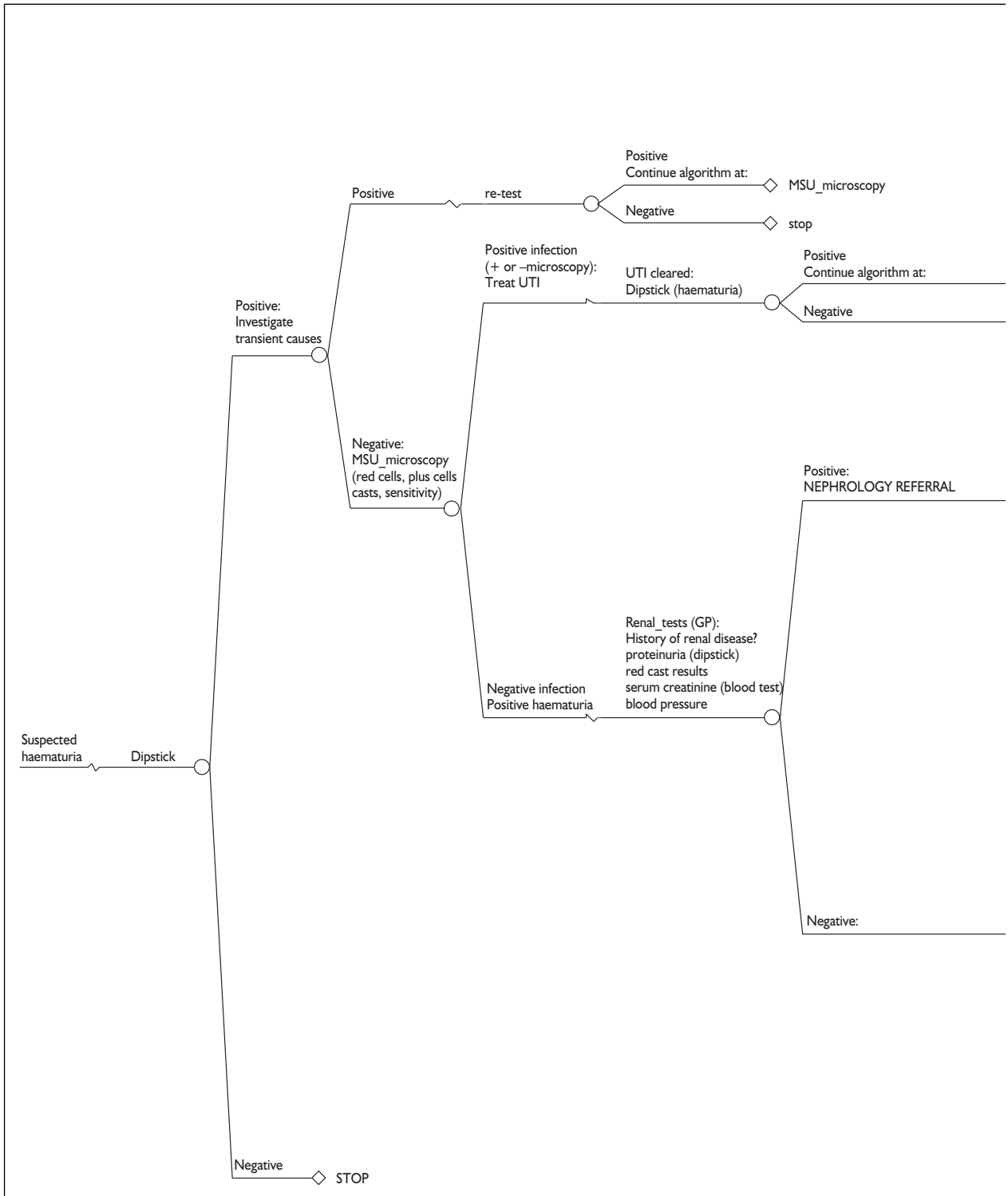
Algorithm of the Scottish Intercollegiate Guidelines Network (SIGN)



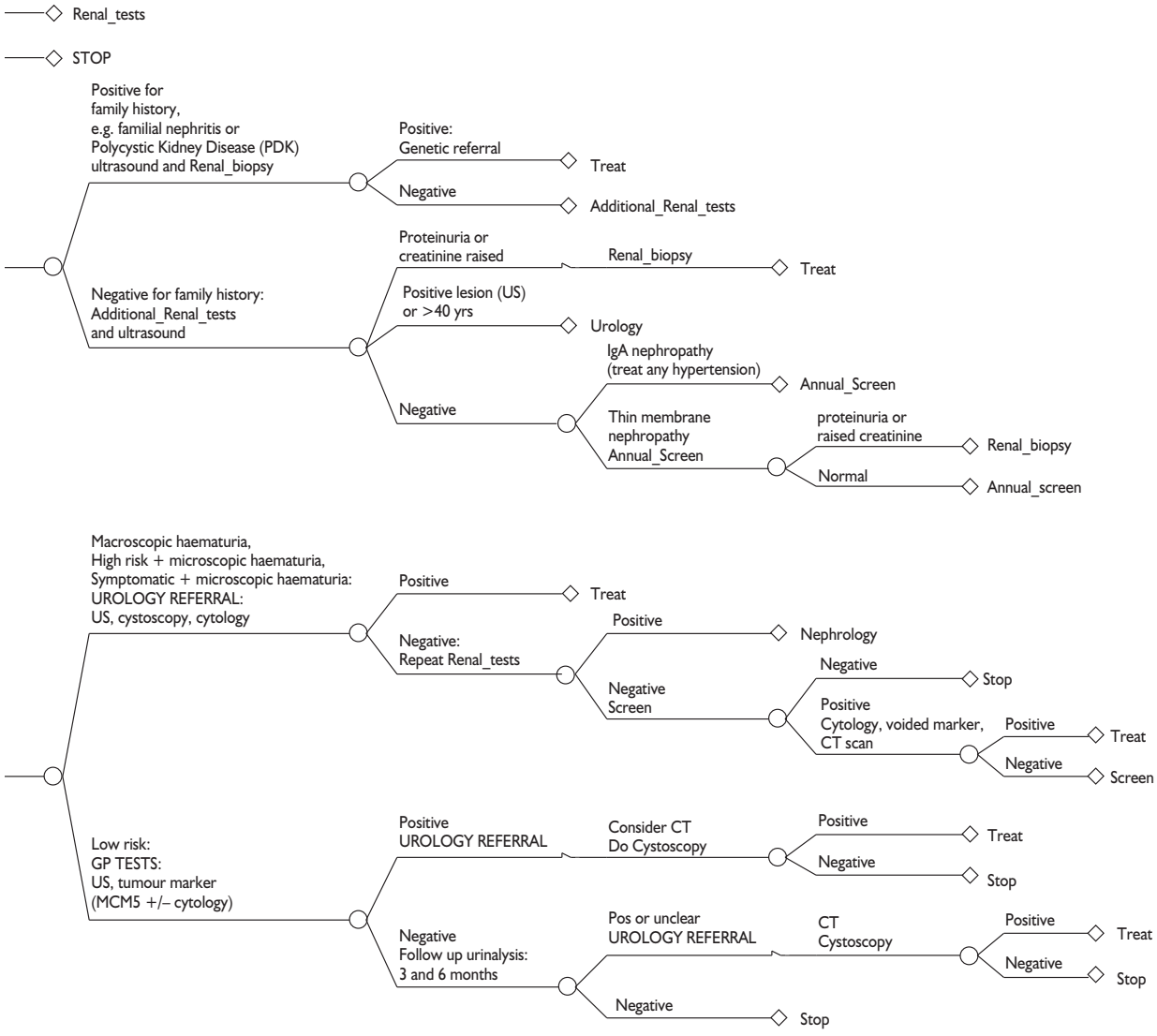
GP_follow_up means patients are followed up by their GP for biennial urinalysis and blood pressure monitoring, refer to appropriate specialist when indicated;
Diagnose_treat means diagnose and treat the detected underlying cause of haematuria; the SIGN recommendations are based on the finding of microscopic haematuria when urinalysis has been undertaken as part of a general examination. They are not designed or intended to advocate population screening; the target group is patients over 13 years of age with haematuria as defined in the algorithm above.

Appendix 12

Algorithm based on consultations with review clinical experts and advisory panel members (J Kelly, TA, JB)



High risk in urology referral means one or more of the following: smoking history, occupational risk, history of gross haematuria, age >40 years, previous urological disorder, history of irritative voiding, recurrent UTI despite antibiotics; Additional_Renal_tests = immunoglobulins; ANA; ANCA; + 24 h urine protein; Annual_Screen means BP and serum creatinine annually; Screen means urinalysis and blood pressure (GP) at 3, 6 and 9 months.



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We look forward to hearing from you.

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