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

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Executive summary

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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.
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 of 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.

Publication

The research findings from the NHS R&D Health Technology Assessment (HTA) Programme directly influence key decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC) who rely on HTA outputs to help raise standards of care. HTA findings also help to improve the quality of the service in the NHS indirectly in that they form a key component of the ‘National Knowledge Service’ that is being developed to improve the evidence of clinical practice throughout the NHS.

The HTA Programme was set up in 1993. Its role is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS. ‘Health technologies’ are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care.

The HTA Programme commissions research only on topics where it has identified key gaps in the evidence needed by the NHS. Suggestions for topics are actively sought from people working in the NHS, the public, service-users groups and professional bodies such as Royal Colleges and NHS Trusts. Research suggestions are carefully considered by panels of independent experts (including service users) whose advice results in a ranked list of recommended research priorities. The HTA Programme then commissions the research team best suited to undertake the work, in the manner most appropriate to find the relevant answers. Some projects may take only months, others need several years to answer the research questions adequately. They may involve synthesising existing evidence or conducting a trial to produce new evidence where none currently exists.

Additionally, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme is able to commission bespoke reports, principally for NICE, but also for other policy customers, such as a National Clinical Director. TARs bring together evidence on key aspects of the use of specific technologies and usually have to be completed within a short time period.

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Reviews in *Health Technology Assessment* are termed ‘systematic’ when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

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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