Update on Haematuria and Bladder Cancer

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Declarations

- None

- Recent changes in TWR
- The problem with Microscopic Haematuria
- The myth of the Haematuria clinic
- Update on bladder cancer management

NICE National Institute for Health and Care Excellence

Referral guidelines for suspected cancer

Issued: June 2005 last modified: April 2011

NICE clinical guideline 27
guidance.nice.org.uk/cg27

National Collaborating Centre for Cancer

Suspected cancer

Suspected cancer:

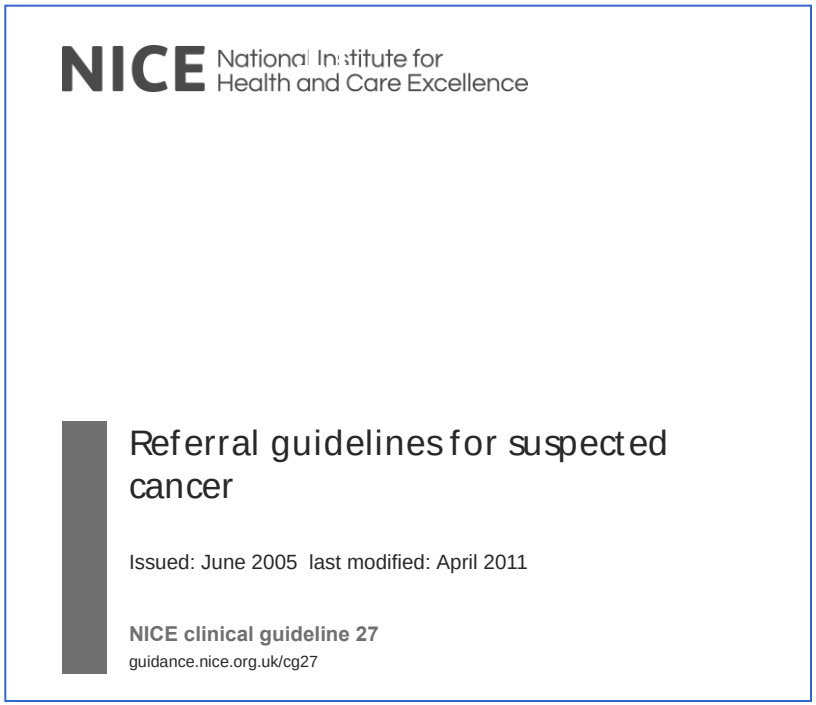
recognition and referral

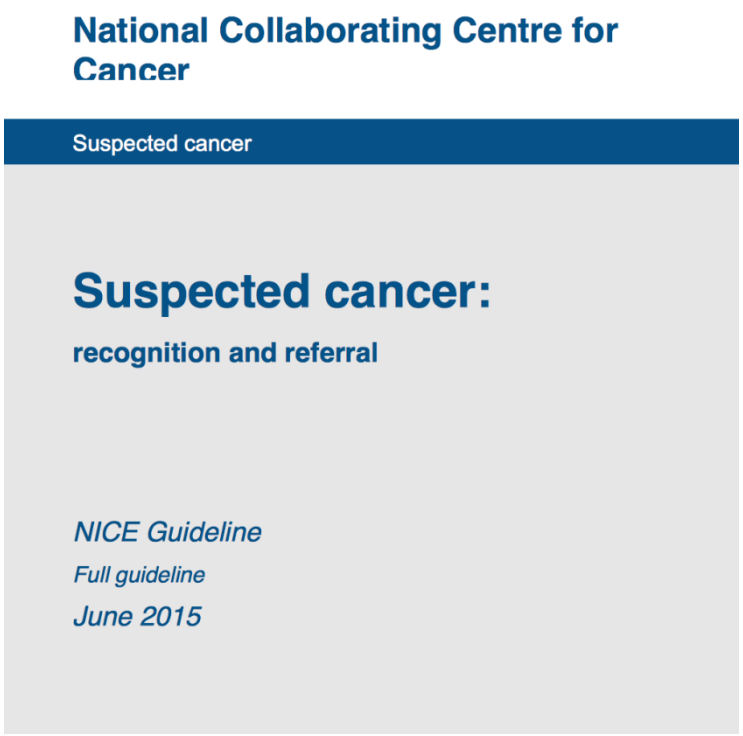
NICE Guideline
Full guideline
June 2015

- of any age with painless macroscopic haematuria C
- aged 40 years and older who present with recurrent or persistent urinary tract infection associated with haematuria C

1.6.4 Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for bladder cancer if they are:

- aged 45 and over and have:
  - unexplained visible haematuria without urinary tract infection **or**
  - visible haematuria that persists or recurs after successful treatment of urinary tract infection,





1.8.12 In patients under 50 years of age with microscopic haematuria, the urine should be tested for proteinuria and serum creatinine levels measured. Those with proteinurea or raised serum creatinine should be referred to a renal physician. If there is no proteinuria and serum creatinine is normal, a non-urgent referral to a urologist should be made.

1.8.13 In patients aged 50 years and older who are found to have unexplained microscopic haematuria, an urgent referral should be made.

Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for bladder cancer if they are aged 60 and over and have unexplained non-visible haematuria and either dysuria or a raised white cell count on a blood test. [new 2015]

CLINICAL REVIEW

Assessment and management of non-visible haematuria in primary care

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Many clinicians are not sure what constitutes clinically relevant haematuria; they are also unsure about when patients with haematuria should be referred for specialist assessment and whether they should be referred to a urologist, nephrologist, or both.

In 2006 the National Institute for Health Research, Health Technology Assessment (NIHR HTA) commissioned a systematic review of the evidence for the investigation of microscopic haematuria, with a view to developing an algorithm for assessing patients in primary care.[1] They concluded that, "Given the paucity of evidence . . . it is not possible to derive an algorithm of the diagnostic pathway for haematuria that would be solely supported by existing evidence." None the less, the investigation of microscopic haematuria is important because serious underlying conditions are present in a proportion of patients.

In the absence of definitive evidence, guidelines based on consensus agreement and expert opinion would be useful and have been proposed.[2-4] However, the terminology and definitions used have not been standardised, so the appropriate baseline assessment of patients is still unclear. In this review, we discuss the rationale for introducing the terms "visible haematuria" and "non-visible haematuria" (symptomatic and asymptomatic) (box 1). The figure shows an algorithm for the assessment of patients with non-visible haematuria.

Initial investigations for patients with symptomatic non-visible haematuria and persistent asymptomatic non-visible haematuria

- Measure plasma creatinine and estimated glomerular filtration rate
- Measure proteinuria—send a random sample of urine for protein:creatinine ratio or albumin:creatinine ratio (according to local practice). Twenty four hour urine collections for protein are rarely needed. 24 hour urine protein or albumin excretion (in mg) can be approximated by multiplying the ratio (in mg/mmol) by 10
- Measure blood pressure

What causes non-visible haematuria?

The presence of non-visible blood in the urine can have a transient or spurious cause; if it persists it may indicate underlying pathology.

Causes of transient non-visible haematuria

The causes of transient non-visible haematuria should be considered and excluded before further assessment (box 2). Transient non-visible haematuria is commonly associated with urinary tract infection, and a repeat dipstick test after treatment for infection will determine whether haematuria is persistent. Urinary tract infection can be the first presentation of important urinary pathology, so recurrent infections are an indication for further investigation, regardless of haematuria.[4-6] Observational studies in athletes confirm that repeated foot striking, such as in long distance running, can cause haematuria,[7] and urine testing should be repeated at least three days after such activity.

Spurious causes

Menstruation can lead to urinary contamination with cyclic cycles, so testing when menstruation has ended is recommended. Discoloration of urine (by drugs or foods) and myoglobin released from necrotic muscle cells (rhabdomyolysis) are other considerations when haematuria is detected on dipstick testing.[4]

Causes of persistent non-visible haematuria

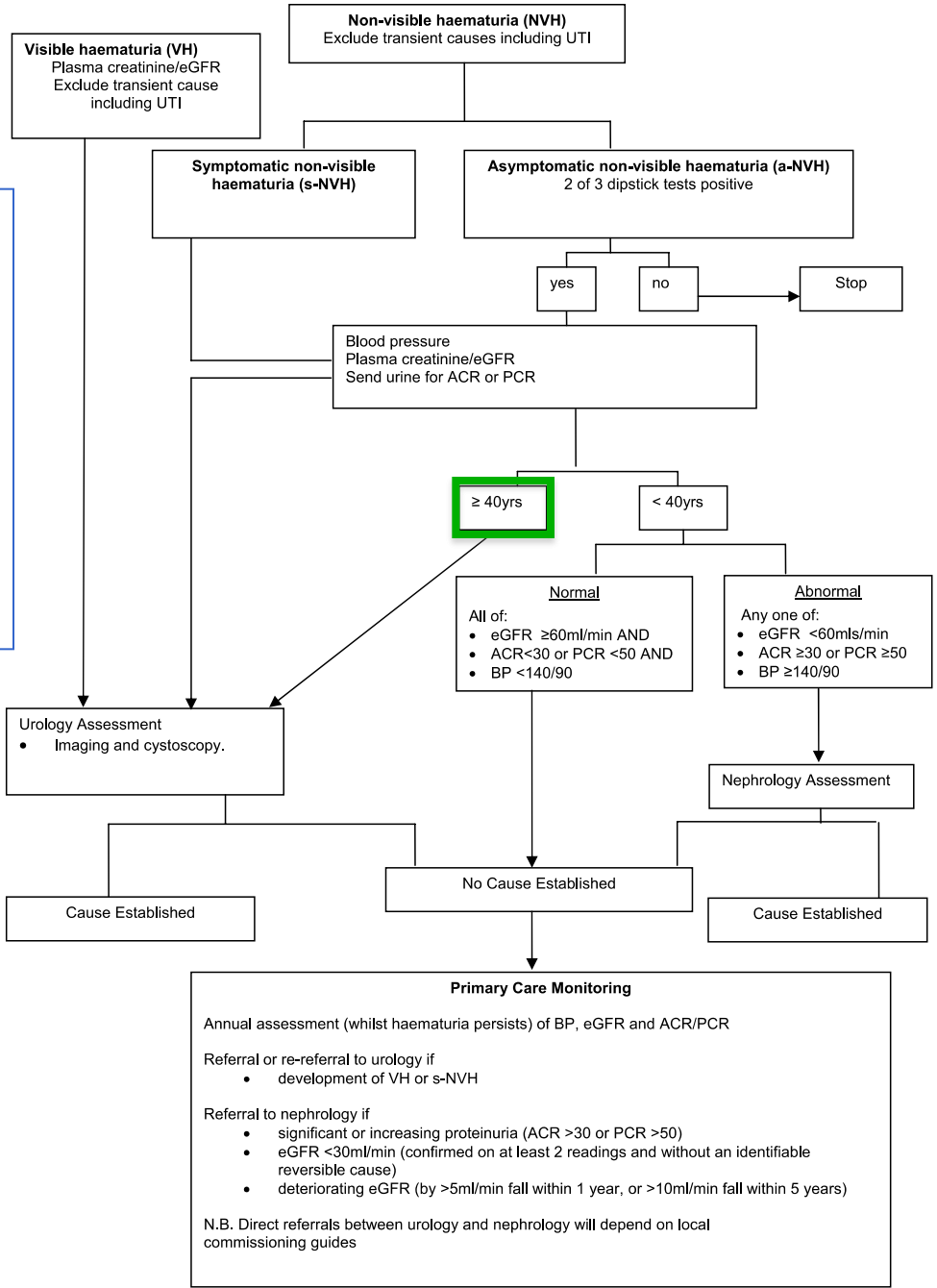
Persistent non-visible haematuria can have urological or nephrological causes (box 2). The most important urological causes include cancer and calculus disease, which are seen in about 5% and 8% of patients, respectively.[8-10] Urothelial cell carcinoma is the most common cancer detected. It is present in about 4% of cases overall but is more prevalent in males and increases with age to 10% in men over 60 with risk factors for disease.[4 11] In young people (<40 years), especially young females, cancer is an uncommon cause of asymptomatic non-visible haematuria, and a glomerular cause is more likely. It is unclear what proportion of patients with haematuria have nephrological as opposed to urological haematuria, because

Joint Consensus Statement on the Initial Assessment of Haematuria

Prepared on behalf of the Renal Association and British Association of Urological Surgeons.

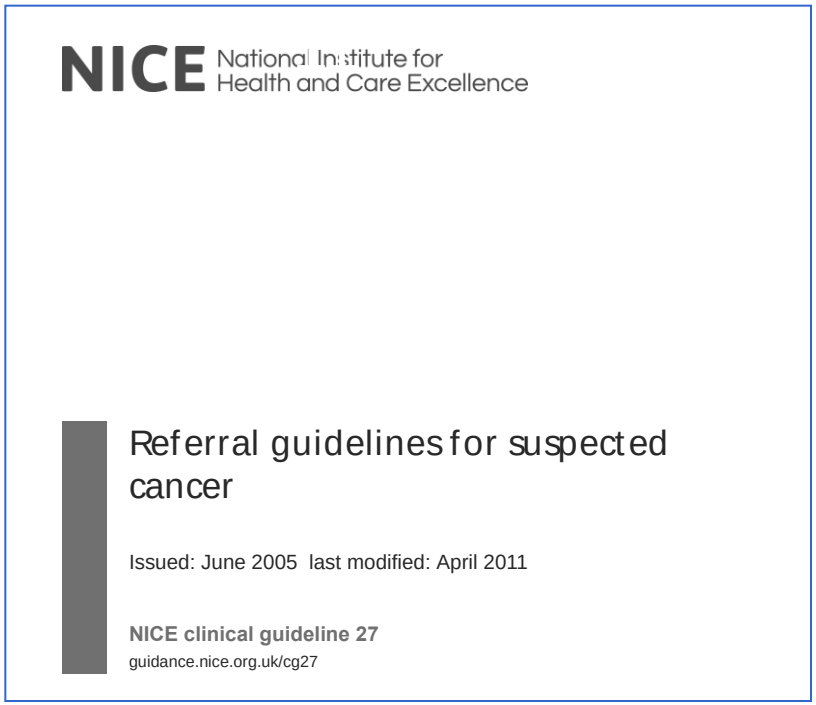
Issue date July 2008

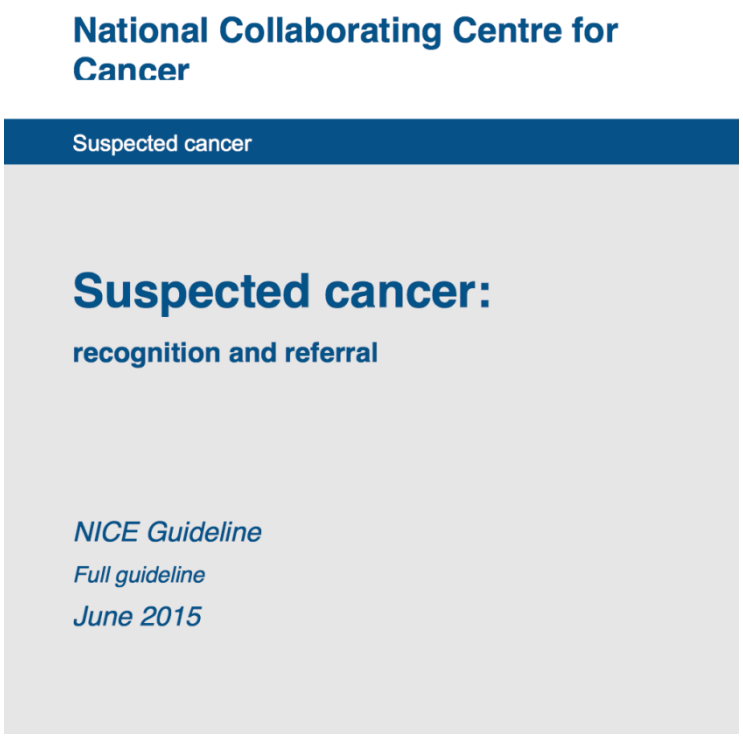
Decision algorithm for the investigation and referral of haematuria.



Risk threshold

- ‘The risk of the patient’s symptoms representing a cancer’
- Used Positive predictive value (PPV)
- Clinicians set 5% PPV across all cancers
- Patient representatives wanted 1%
- Settled on 3% - ‘A considerable liberalisation’





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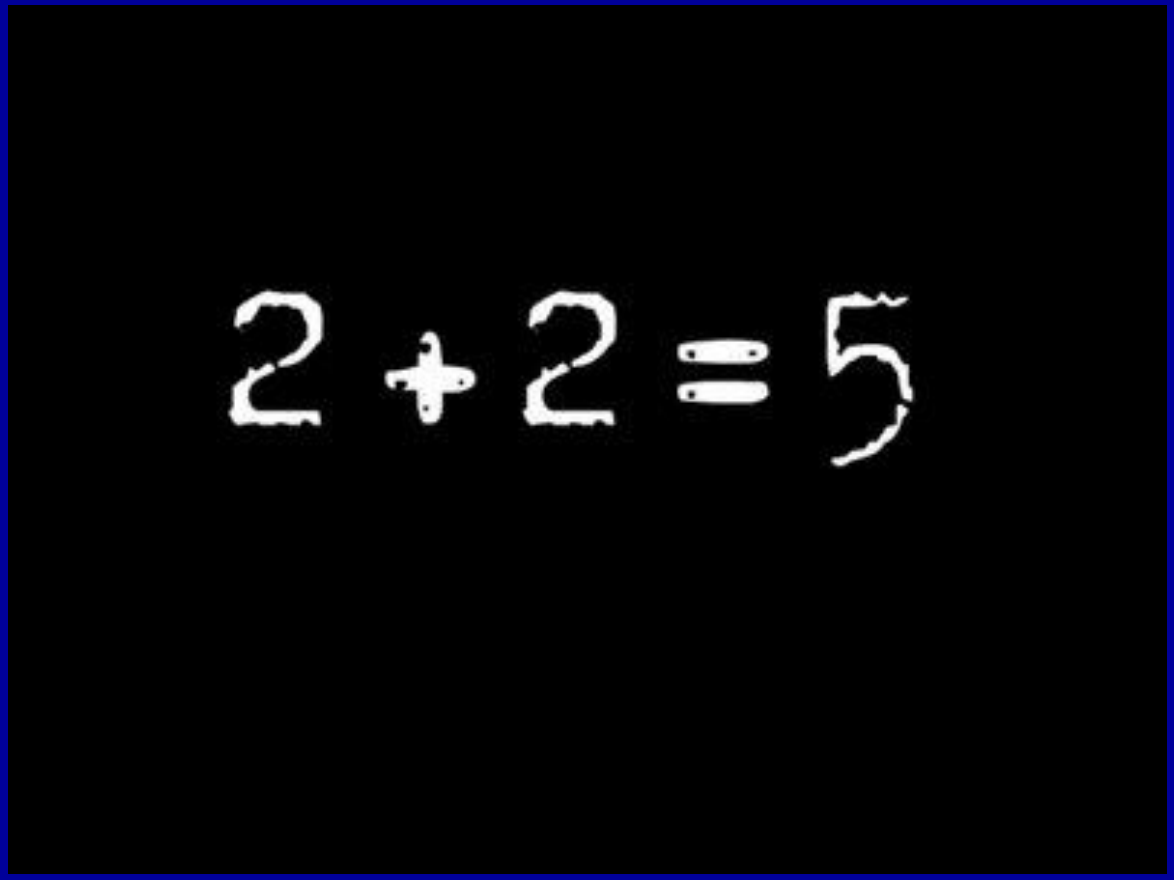
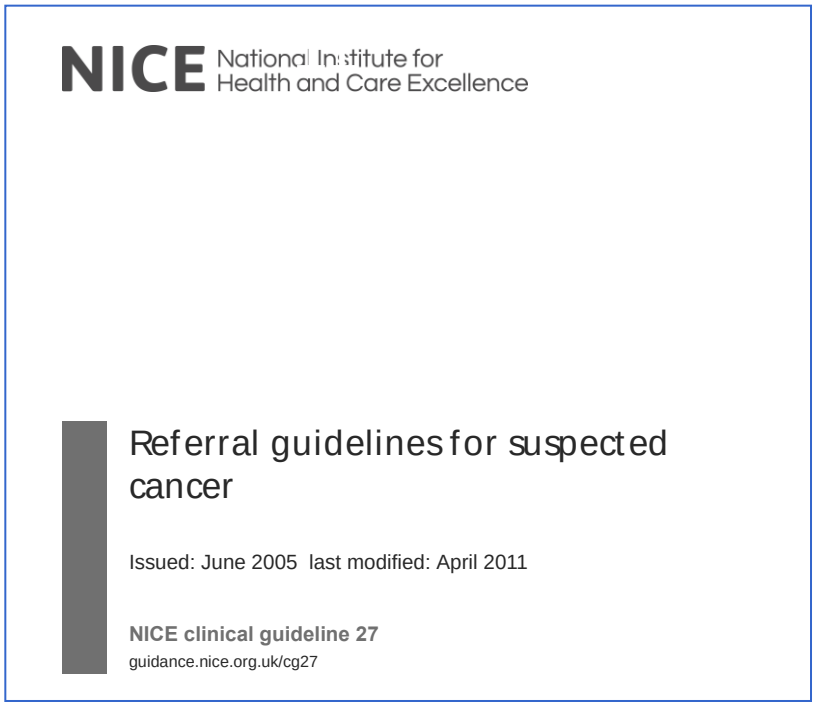
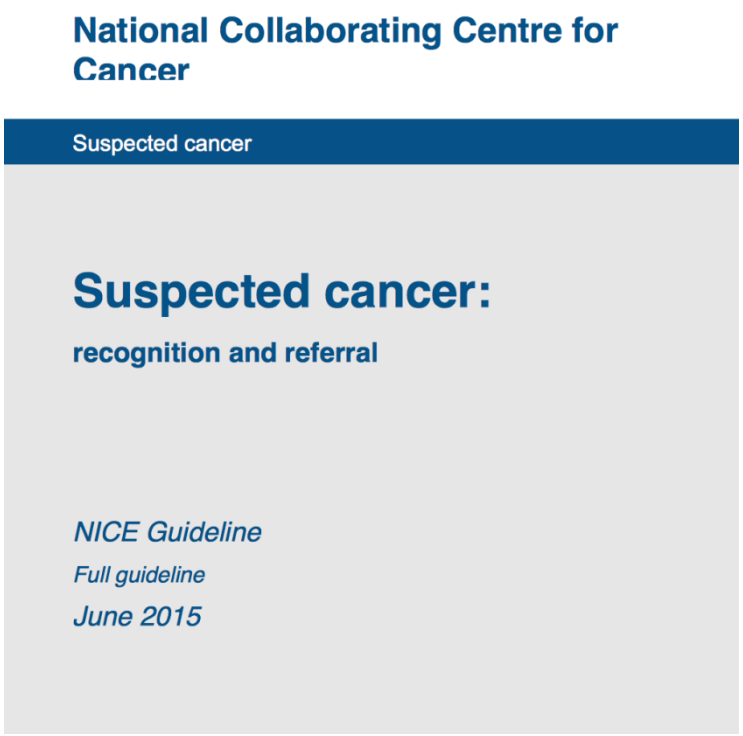
Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for bladder cancer if they are aged 60 and over and have unexplained non-visible haematuria and either dysuria or a raised white cell count on a blood test. [new 2015]


2+2=5





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Studies included	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
Bruyninckx (2003), Collins (2013),	Haematuria	All patients (N = 70330)	4.43 (2.48-7.79)
Friedlander (2014), Hippisley-Cox (2012), Jones (2007, at 6 months)			
Bruyninckx (2003), Collins (2013), Friedlander (2014), Hippisley-Cox (2012), Jones (2007, at 3 years)	Haematuria	All patients (N = 70330)	4.72 (2.63-8.32)

But lets look more closely….

The GDG also noted that most of the evidence did not distinguish between visible and non-visible haematuria, but largely grouped these two symptoms together as haematuria. The GDG judged, based on their clinical experience, that most of that evidence was likely to reflect visible haematuria which left them with evidence from one paper about non-visible haematuria.

Price (2014)	Non-visible haematuria (coded and uncoded data)	Patients 40-59 years	0.79 (0.11-5.6)
Price (2014)	Non-visible haematuria (coded and uncoded data)	All patients ≥ 60 years	1.6 (1.2-2.1)

5000pts = 7% of the sample

Urine Dipstick

- Sensitivity 0.91 and Specificity 0.99 for MH
- BUT –
  - 16-24% of population have MH
  - 33% of BC patients don’t have any haematuria

How is MH defined by NICE?

- Its not !

Trace versus 1+

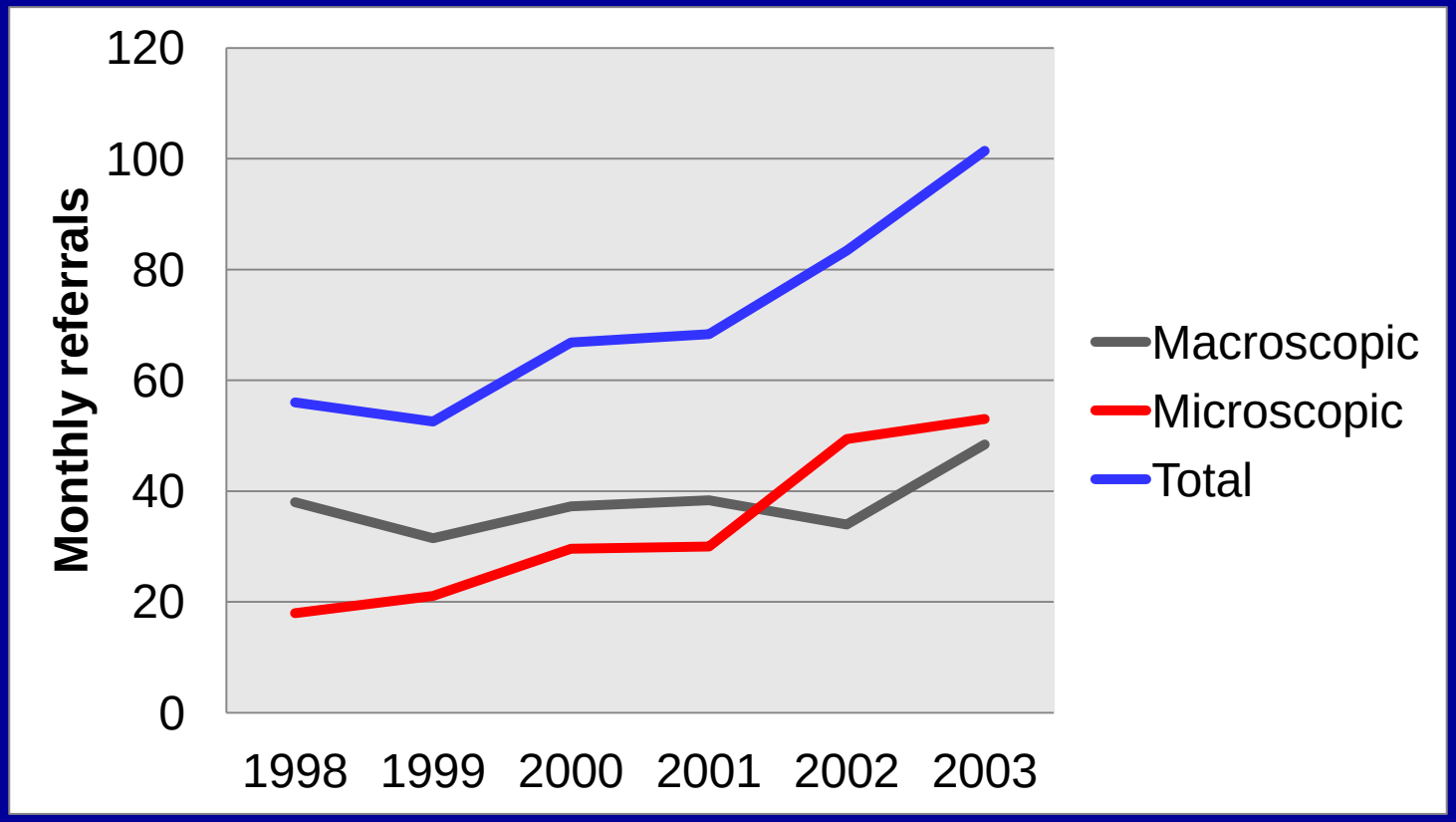
- Whilst the sensitivity of urine dipsticks may vary from one manufacturer to another, significant haematuria is considered to be 1+ or greater. Trace haematuria should be considered negative.

Haemolysed versus non-haemolysed

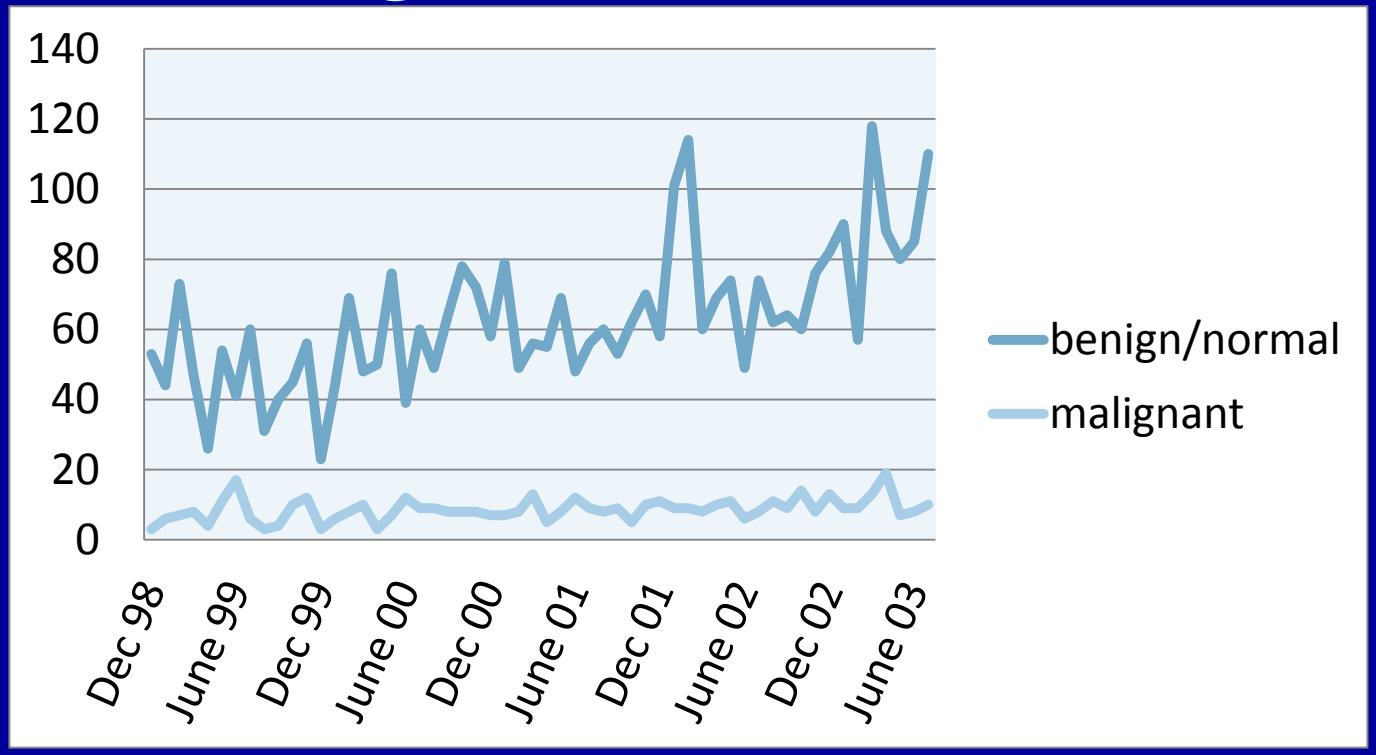
- There is no distinction in significance between non-haemolysed and haemolysed dipstick-positive haematuria. 1+ positive for either should be considered of equal significance.

c) Persistent a-NVH (in absence of UTI or other transient causes). Persistence is defined as 2 out of 3 dipsticks positive for NVH.

VH and NVH referrals

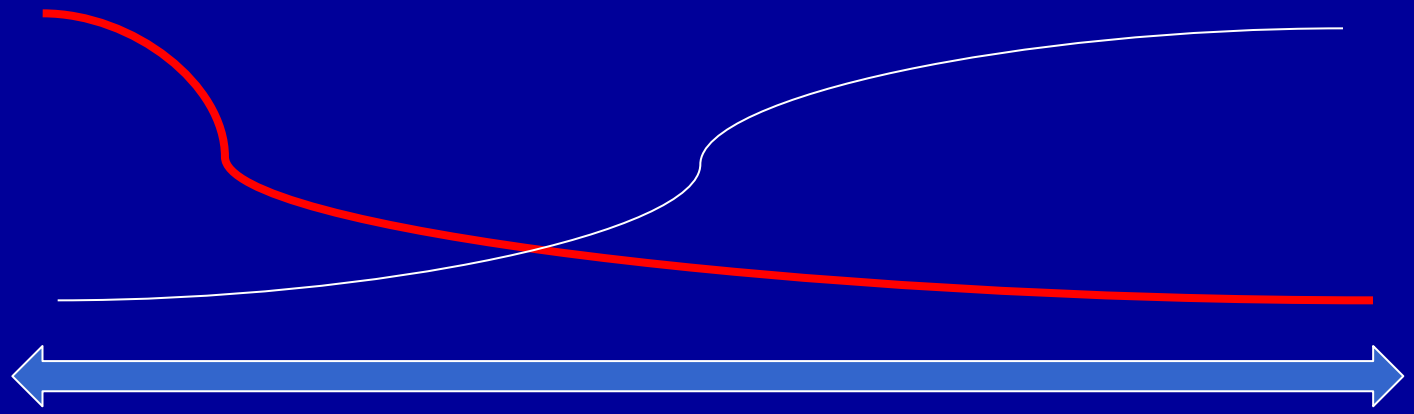


Change in detection rate



- Referrals to Haematuria clinic
  - Was 2/3 Macro, 1/3 Microscopic
  - Now reversed with 2/3 micro
  - 1200/year at RSCH and rising
  - Annual cost to NHS £33M
  - 1/3 of the £100M cost of *treating* Bladder Ca

The haematuria problem…



74 yo male smoker
with frank haematuria

40 year old female
N/S incidental
finding

Education and debate

Time to abandon testing for microscopic haematuria in adults?

Per-Uno Malmström

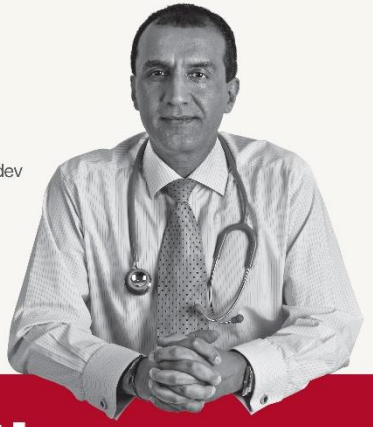
Although there is no doubt that macroscopic haematuria is serious, the clinical significance of asymptomatic microscopic haematuria is controversial. Should it still be tested for?

Summary points

- Microhaematuria is poorly predictive of cancers of the urinary tract
- Haemoglobin dipstick testing is not a reliable way of detecting early bladder cancer in patients at high risk
- Microhaematuria is not reliable evidence of a stone in the ureter and may be misleading, as it is often present in other serious conditions that cause acute loin pain
- Testing for microhaematuria is not helpful in evaluating men with lower urinary tract symptoms

NHS

Dr Anant Sachdev



If you notice blood in your pee, even if it's 'just the once', tell your doctor.

It could be an early sign of kidney or bladder cancer. Finding it early makes it more treatable, so tell your doctor straight away.

BE CLEAR ON CANCER

nhs.uk/bloodinpee

Investigations in primary care

No primary care evidence was identified pertaining to the diagnostic accuracy of urine cytology, ultrasound, cystoscopy, blood HCG, urine marker NMP22, and urine marker MCM5 in patients with suspected bladder cancer where the clinical responsibility was retained by primary care.

The haematuria clinic: Fit for purpose?

‘The haematuria clinic is there to detect urological cancer’

Findings at a Haematuria clinic

	Incidence %
Bladder cancer (macroscopic haematuria)	19
UTI	13
Nephrological Disease	10
Urinary Calculi	8.4
Bladder cancer (microscopic haematuria)	5
Renal Cell Ca	1.9
Upper tract TCC	0.3
Primary carcinoma in situ	0.3

The haematuria Clinic: Fit for purpose?

‘Bladder cancer patients present with haematuria’

Presentation of bladder cancer

Symptom	N	%
Frank Haematuria	162	67
Pure LUTS	20	8
Chance	14	6
Symptomatic Microscopic Haematuria	10	4
Symptoms of UTI	8	3
Clear delay in reporting FH	5	2
Gynae bleeding	4	2
Malaise	4	2
Non-specific Sx	4	2
Asymptomatic Microscopic Haematuria	3	1
Incontinence	2	1
Recurrent UTIs	2	1
Anaemia	2	1
	240	100

Are we barking up the wrong tree?

IS IT TIME TO RE-DESIGN THE HAEMATURIA CLINIC?

Hugh Mostafid, Raj Persad*, Roger Kockelbergh† and Derek Fawcett† – Department of Urology, North Hampshire Hospital, Basingstoke, Hampshire, *Department of Urology, Bristol Royal Infirmary, Bristol, †Department of Urology, Leicester General Hospital, Leicester, and †Department of Urology, Royal Berkshire Hospital, Reading, UK

Accepted for publication 9 September 2009

Finding	Incidence, %
Bladder cancer (macroscopic haematuria)	19
UTI	13
Nephrological disease	10
Urinary calculi	8.4
Bladder cancer (microscopic haematuria)	5
RCC	1.5
Upper tract TCC	0.3
Primary carcinoma *in situ*	0.3

TABLE 1
Incidence of findings in a haematuria clinic [2,3]

Haematuria Referrals

	Risk of Bladder cancer	% of pts with bladder Ca	Referral route
Macroscopic Haematuria	19%	67%	TWR to one stop haematuria clinic
Symptomatic Micro. haematuria	5	4%	OPD
Asymptomatic micro. haematuria	<5%	1%	OPD?

Update on bladder cancer

- NMIBC not ‘superficial’
- NICE Bladder Cancer Guidelines
- BCG shortage
- Centralisation of radical cystectomy

Eliminate the Term "Superficial" Bladder Cancer

Alan M. Nieder and Mark S. Soloway
Department of Urology
University of Miami Miller School of Medicine
Miami, Florida

1.3 Treating non-muscle-invasive bladder cancer

1.3.1 **Risk classification in non-muscle-invasive bladder cancer**

- Ensure that for people with non-muscle-invasive bladder cancer all of the following are recorded and used to guide discussions, both within multidisciplinary team meetings and with the person, about prognosis and treatment options:
- recurrence history
- size and number of cancers
- histological type, grade, stage and presence (or absence) of flat urothelium, detrusor muscle (muscularis propria), and carcinoma in situ
- the risk category of the person's cancer
- predicted risk of recurrence and progression, estimated using a risk prediction tool.

- Low
- Intermediate
- High

1.4 Follow-up after treatment for non-muscle-invasive bladder cancer

Low-risk non-muscle-invasive bladder cancer

1.4.3

Offer people with low-risk non-muscle invasive bladder cancer cystoscopic follow-up 3 months and 12 months after diagnosis.

1.4.4

Do not use urinary biomarkers or cytology in addition to cystoscopy for follow-up after treatment for low-risk bladder cancer.

1.4.5

Discharge to primary care people who have had low-risk non-muscle-invasive bladder cancer and who have no recurrence of the bladder cancer within 12 months.

1.4.6

Do not offer routine urinary cytology or prolonged cystoscopic follow-up after 12 months for people with low-risk non-muscle-invasive bladder cancer.

Centralisation of Bladder Cancer

- Pelvic cancer centre for 1.8 million
- ~ 80 cystectomies a year
- 2 robotic cystectomies per week
- Improved outcomes – Discharged at D5 cf. D14, ↓ B.Tx