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Haematuria

Dr Jon Rees

Tyntesfield Medical Group, North Somerset

www.primarycareurologysociety.org

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Declaration of Interests

- Jon Rees has received Consultancy and Speaker fees for Ferring and Astellas and is Chair of PCUS

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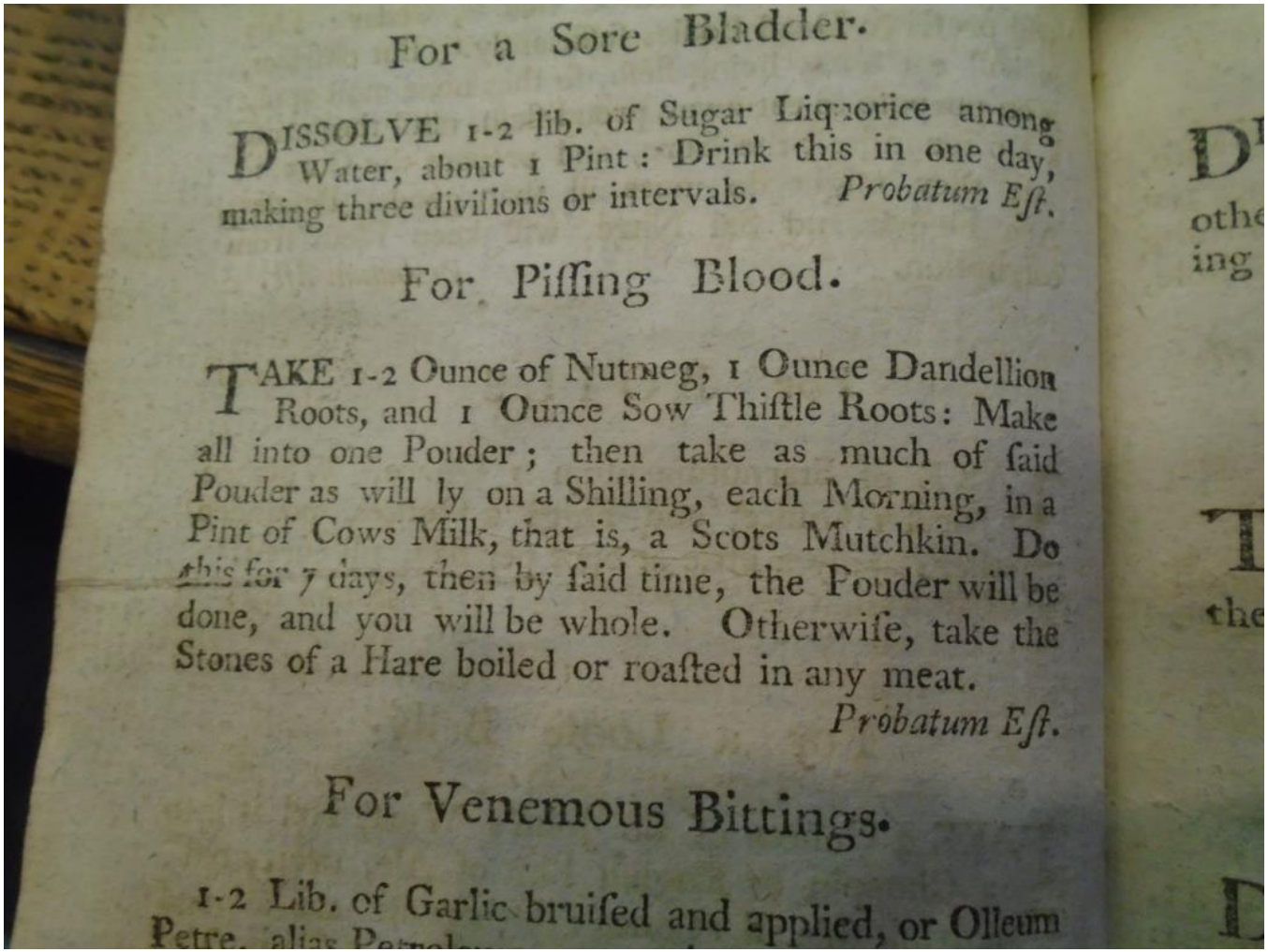

For a Sore Bladder.

DISSOLVE 1-2 lib. of Sugar Liquorice among Water, about 1 Pint: Drink this in one day, making three diviſions or intervals. *Probatum Eſt.*

For Piſſing Blood.

TAKE 1-2 Ounce of Nutmeg, 1 Ounce Dandellion Roots, and 1 Ounce Sow Thiſtle Roots: Make all into one Pouder; then take as much of ſaid Pouder as will ly on a Shilling, each Morning, in a Pint of Cows Milk, that is, a Scots Mutchkin. Do this for 7 days, then by ſaid time, the Pouder will be done, and you will be whole. Otherwiſe, take the Stones of a Hare boiled or roaſted in any meat.

Probatum Eſt.

For Venemous Bittings.

1-2 Lib. of Garlic bruiſed and applied, or Olleum Petre, alias Petrol

Referrals to Haematuria Clinic

- 50:50 between Macro and Microscopic
- Annual cost to NHS £33M
- **1/3 of the £100M cost of *treating* Bladder Ca**

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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

Terminology

- Macroscopic / Frank / Gross = VISIBLE haematuria
- Microscopic / Dipstick = NON-VISIBLE haematuria
- Symptomatic non-visible haematuria = plus LUTS or upper urinary tract symptoms e.g. loin pain (versus Asymptomatic)

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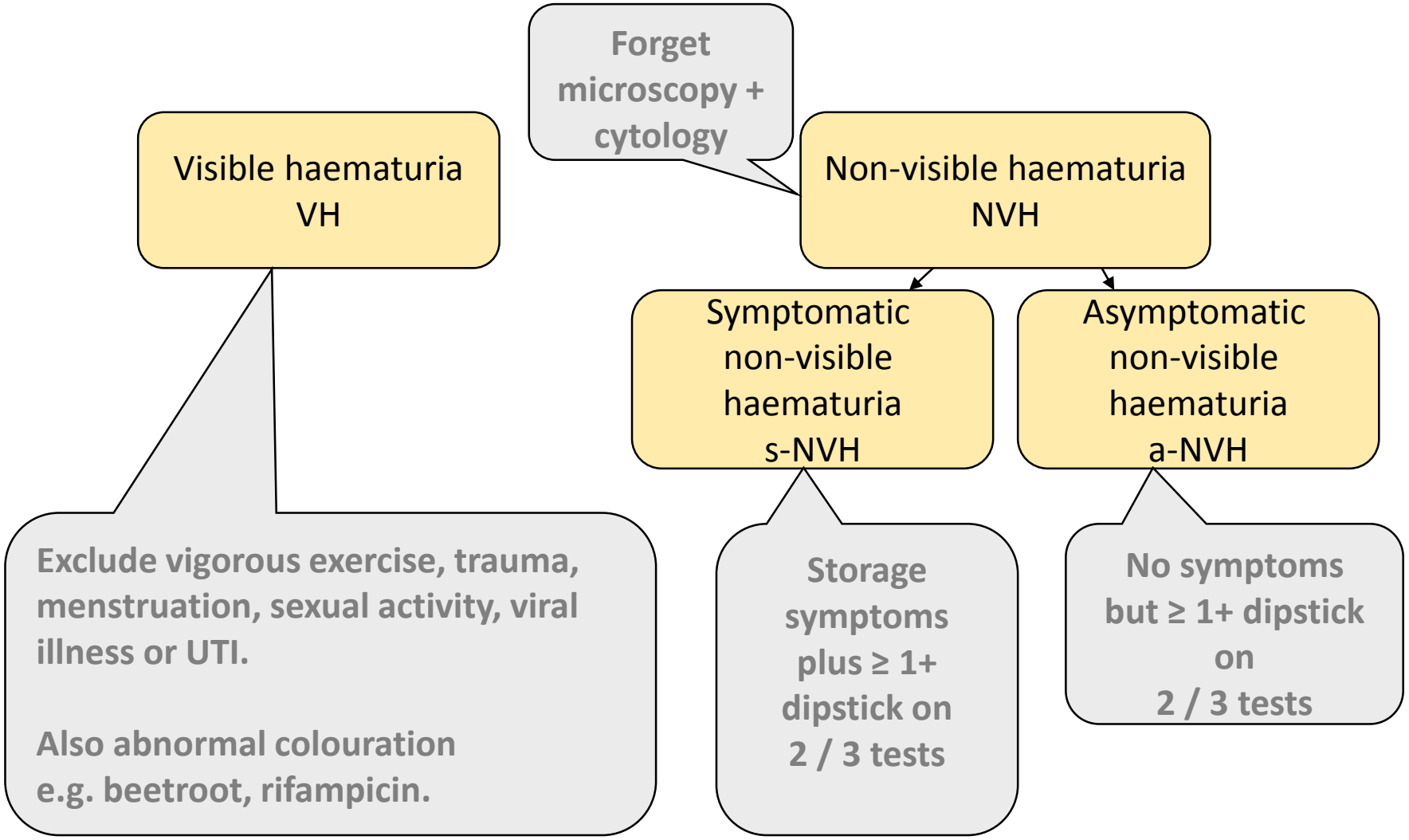
Terminology



Who to test: Prevalence of NVH

- Approximately 2.5% of general population
- If population screened pick up rate of significant diagnosis only 1.5%
- So …

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Who to test: Indications for a urine dipstick

- LUTS or Upper UT symptoms
- Diagnosis of hypertension
- Diabetes (annual)
- Newly discovered proteinuria
- Newly detected CKD (eGFR<60)
- Multisystem disease with suspected renal involvement

Diagnosis of haematuria

- No evidence for screening
- Exclude transient causes e.g. UTI
- Urine dipstick '+' or more – MSU only to exclude infection
- Symptomatic non-visible haematuria warrants further assessment on single episode
- Asymptomatic non-visible haematuria confirm on 2 out of 3 tests e.g. 'persistent'

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Visible haematuria

- Malignancy relatively common (20 – 25%)
- This study:
  - 72% no disease
  - 16.5% TCC bladder
  - 2% RCC
  - 0.5% UT TCC
  - 9% Stone

Edwards et al, BJU Int 2006

Non-visible haematuria

- Malignancy much less common (3 - 5%)
- This study:
  - 87% no disease
  - 4% TCC bladder
  - 1% RCC
  - 0.1% UT TCC
  - 8% Stone

A prospective analysis of the diagnostic yield resulting from the attendance of 4020 patients at a protocol-driven haematuria clinic

TOM J. EDWARDS, ANDREW J. DICKINSON, SALVATORE NATALE, JANE GOSLING and JOHN S. MCGRATH
Urology, Derriford NHS Trust, Plymouth, Devon, UK

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OBJECTIVE

To clarify the prevalence of disease as determined by age, sex and the degree of haematuria at presentation, and to ascertain the merits of using ultrasonography (US), i.v. urography (IVU) or both when imaging the upper urinary tract, in a prospective cohort of patients attending a protocol-based haematuria clinic.

PATIENTS AND METHODS

In a two-tier protocol, as a part of first-line investigation, all 4020 patients attending the clinic between October 1998 and August 2003 had US and flexible cystoscopy. Subsequently, IVU was used where indicated following abnormal first-line tests and in patients with persistent haematuria where no abnormality had been detected.

RESULTS

In all, 2627 men and 1393 women presented with microscopic (52.2%) or macroscopic haematuria (47.8%). The overall prevalence of malignant disease was 12.1%, but for macroscopic haematuria it was 18.8% and for microscopic haematuria 4.8%. Age and sex also influenced the observed rates of disease. Of the upper tract tumours, 70 were identified after abnormal US, with three cases of transitional cell carcinoma identified on IVU after a normal US.

CONCLUSIONS

The study provides a rationale for the appropriate investigation of all patients, moderated by the age, sex and degree of haematuria, and the ubiquitous use of US with selective IVU based on age, sex and degree of (and persistence of) haematuria.

KEYWORDS

haematuria, IVU, ultrasonography, cancer, upper tract, diagnosis

INTRODUCTION

From population screening it was estimated that the prevalence of haematuria, both macroscopic and microscopic, may range from 5% [1] to as high as 20% [2,3], depending on the subgroup. The convenience of urine dipstick testing has increasingly facilitated the detection of haematuria. Based on the presumption that detection of any degree of haematuria represents an opportunity for the diagnosis of treatable occult pathology, current guidelines in the UK recommend investigation of both macroscopic and microscopic haematuria [4]. Consequently, this patient group has come to represent a considerable proportion of urological referrals.

Despite this increasing workload, consensus has yet to be reached on two keys aspects of the management of these patients, i.e. the thresholds for investigation, in terms of patient age and mode of presentation (microscopic vs macroscopic haematuria [5]), and the choice of imaging method for the upper tract (UT). This is shown by the wide variation in investigative protocols, not only within the UK, but also among countries in Europe and the USA [6,7]. In the latter, isolated microscopic haematuria is much less likely to be investigated with the same urgency as macroscopic haematuria. The AUA recommends investigation only in patients who have had three or more red blood cells on two of three properly collected specimens. These differences in approach to the investigation of haematuria are due, in part, to a lack of robust data on the likelihood of finding disease within age-specific or presentation-specific groups [8]. Furthermore, the relative merit of ultrasonography (US) compared with IVU, or indeed the need for dual-method (or alternative) imaging, is unresolved [9,10]. This lack of data hampers both the construction of evidence-based protocols and the identification of high-risk subgroups, i.e. those who would otherwise benefit from targeted investigation.

In reporting the largest consecutive prospective series of patients investigated for the presence of haematuria in a protocol-driven clinic to date, we aim to clarify the likelihood of detecting disease within this population, the mode of detecting UT lesions and, consequently, the additional contribution of the IVU in the presence of a normal US.

PATIENTS AND METHODS

The outcomes of all investigations undertaken on consecutive patients attending a protocol-driven, 'one-stop' haematuria clinic in a large teaching hospital, between October 1998 and August 2003, were recorded (catchment population 400 000).

Non-urological clinicians, primarily GPs, referred patients once UTI had been excluded. Investigations were conducted according to a local protocol encompassing recognized guidelines (Fig. 1). After obtaining a history, an examination, blood pressure measurement, serum creatinine and urea estimation, all patients had first-line imaging of the urinary UT. This comprised a plain abdominal

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Edwards et al, BJU Int 2006

Risk of malignancy in non-visible haematuria

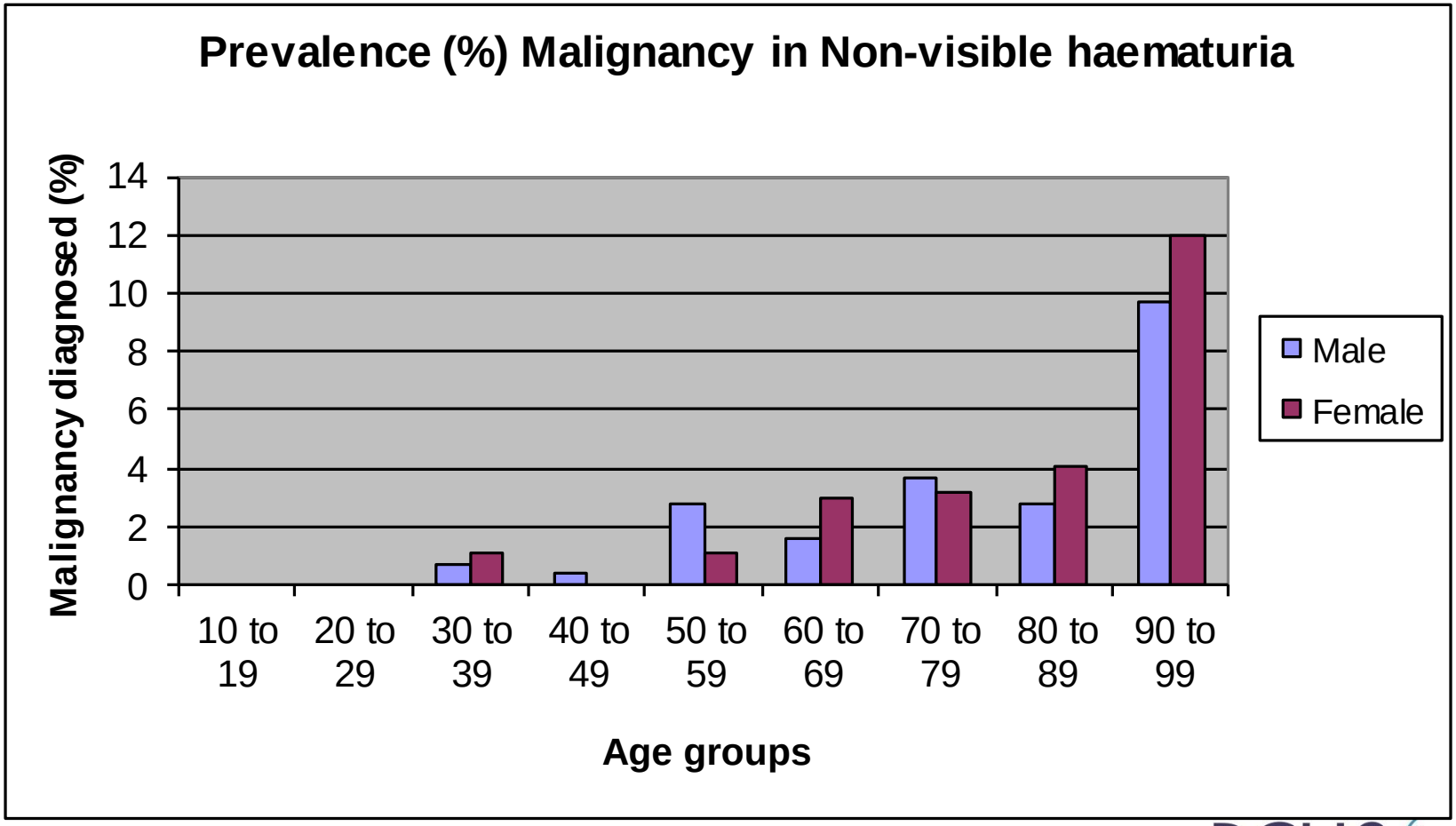
- In men under 50 years old:

0.44%

- In women under 60 years old:

0.75%

Risk of malignancy in non-visible haematuria



Edwards et al, BJU Int 2006, based on 4020 patients at haematuria clinic

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Causes of NVH

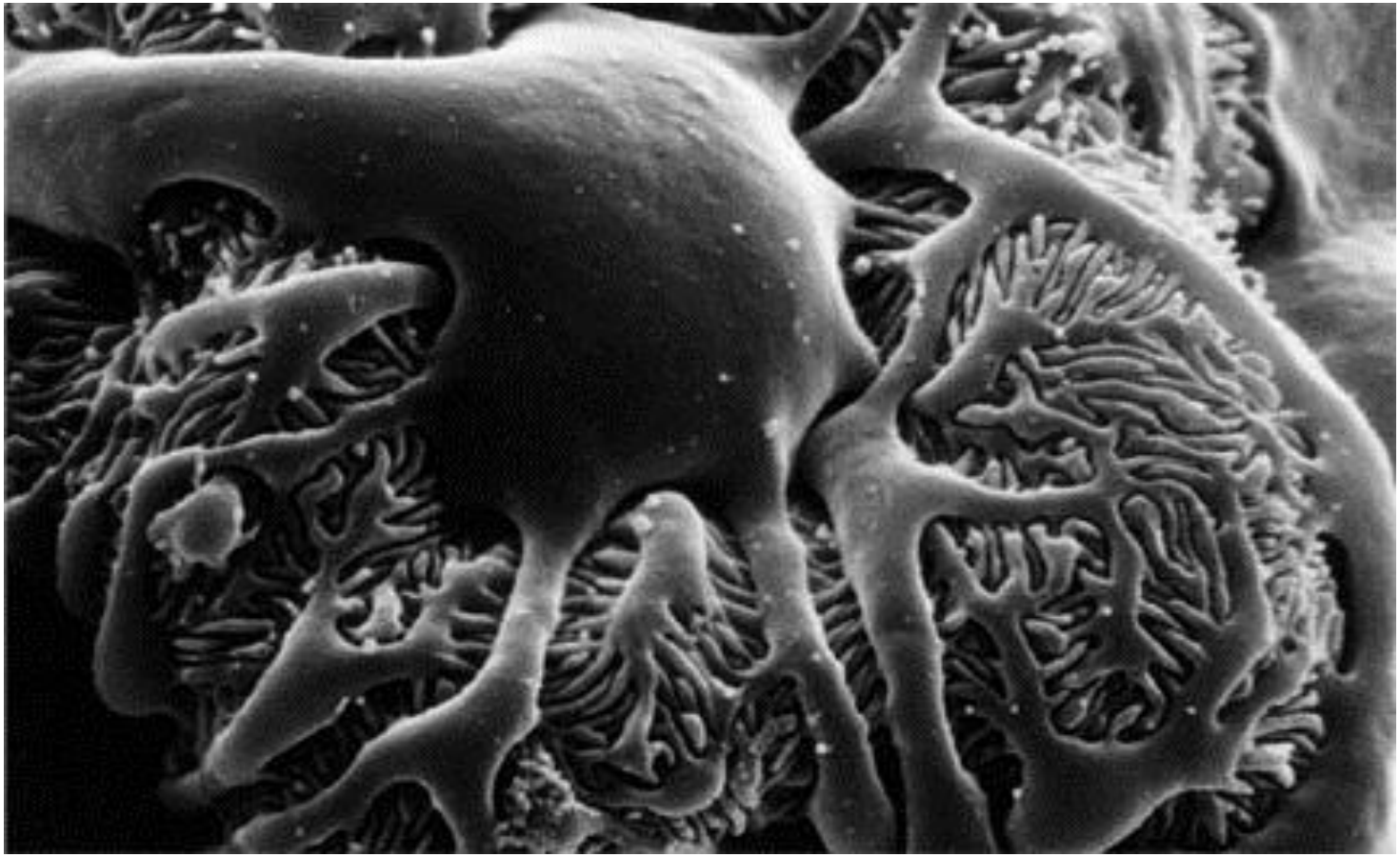
Urological causes

- **Common:**
  - **BPH**
  - **Cancer (bladder, renal, prostate, ureter)**
  - **Calculus disease**
  - **Cystitis / pyelonephritis**
  - Schistosomiasis
- Less Common:
  - Radiation cystitis
  - Urethral strictures
  - TB
  - Medullary sponge kidney
  - Polycystic kidney disease
  - Loin pain haematuria syndrome

Nephrological causes

- **Common:**
  - **Thin basement membrane disease**
  - **IgA Nephropathy**
- Less common:
  - Lupus nephritis
  - Vasculitis
  - HSP
  - Goodpastures syndrome
  - Haemolytic uraemic syndrome
  - Alport's syndrome
  - Nail patella syndrome
  - Chronic primary glomerulonephritis

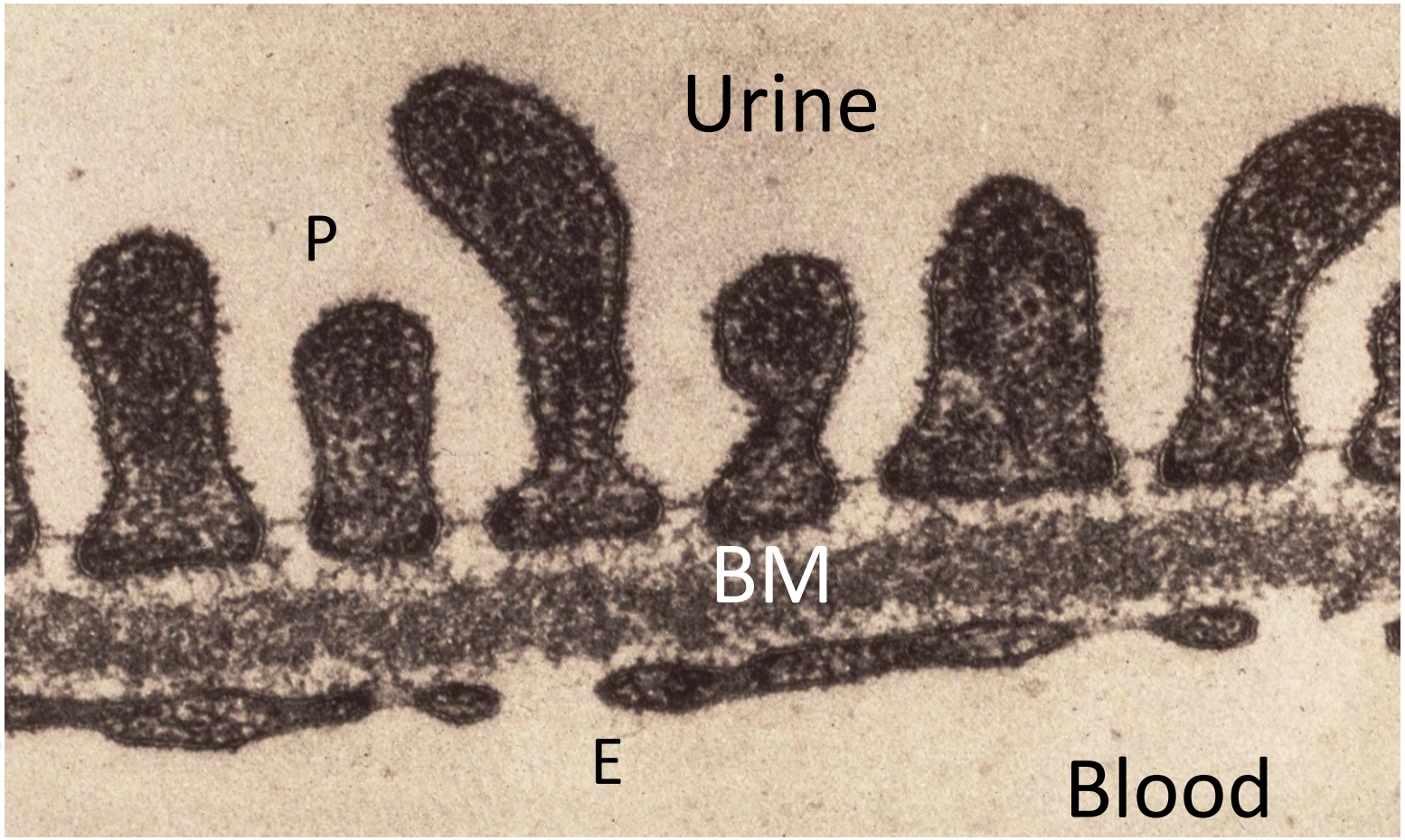
The Podocyte



Thin basement membrane syndrome

BM usually ~450µm.

In TBMS it is reduced to ~150µm.



Thin Basement Membrane disease

- AKA ‘Benign familial haematuria
- Presents with non-visible haematuria
- Renal function, blood pressure, protein excretion all normal
- No risk to long term renal function so diagnosis not usually confirmed by biopsy

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IgA Nephropathy (Berger's)

- Immunoglobulin deposited in kidneys
- Usually follows simple viral URTI
- Often presents initially with VH, then persistent NVH
- Progresses to chronic renal failure in 25% over 20 years

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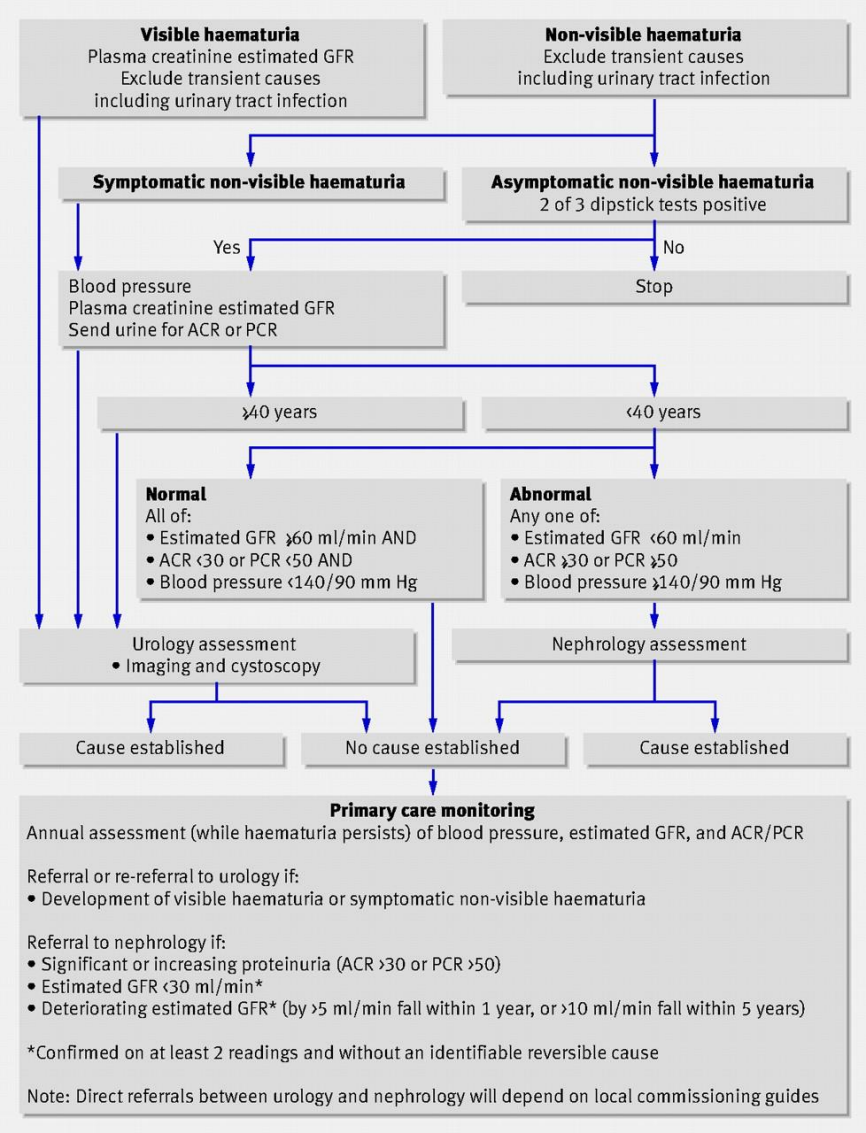
Decision algorithm for the investigation of non-visible haematuria and the referral criteria adopted by the British Association of Urological Surgeons and the Renal Association



Kelly, J. D et al. BMJ 2009;338:a3021

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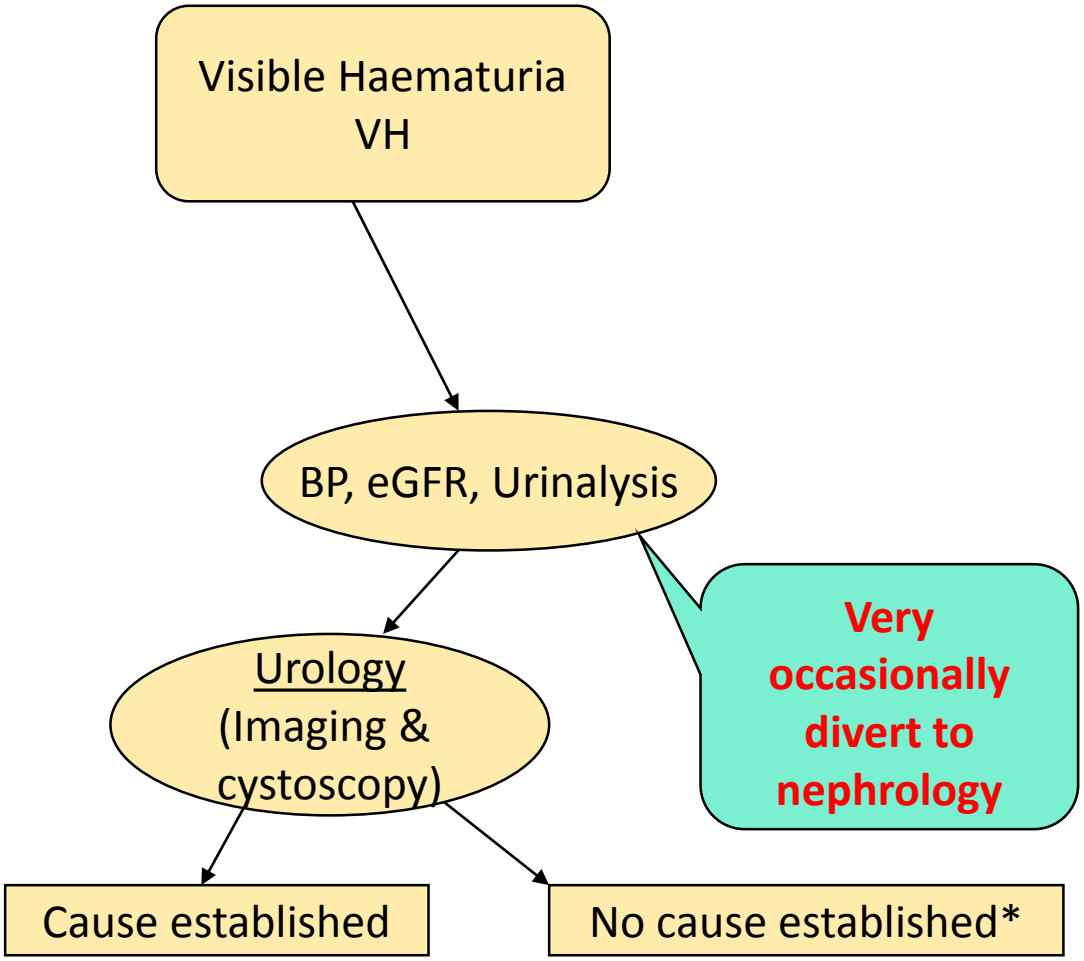
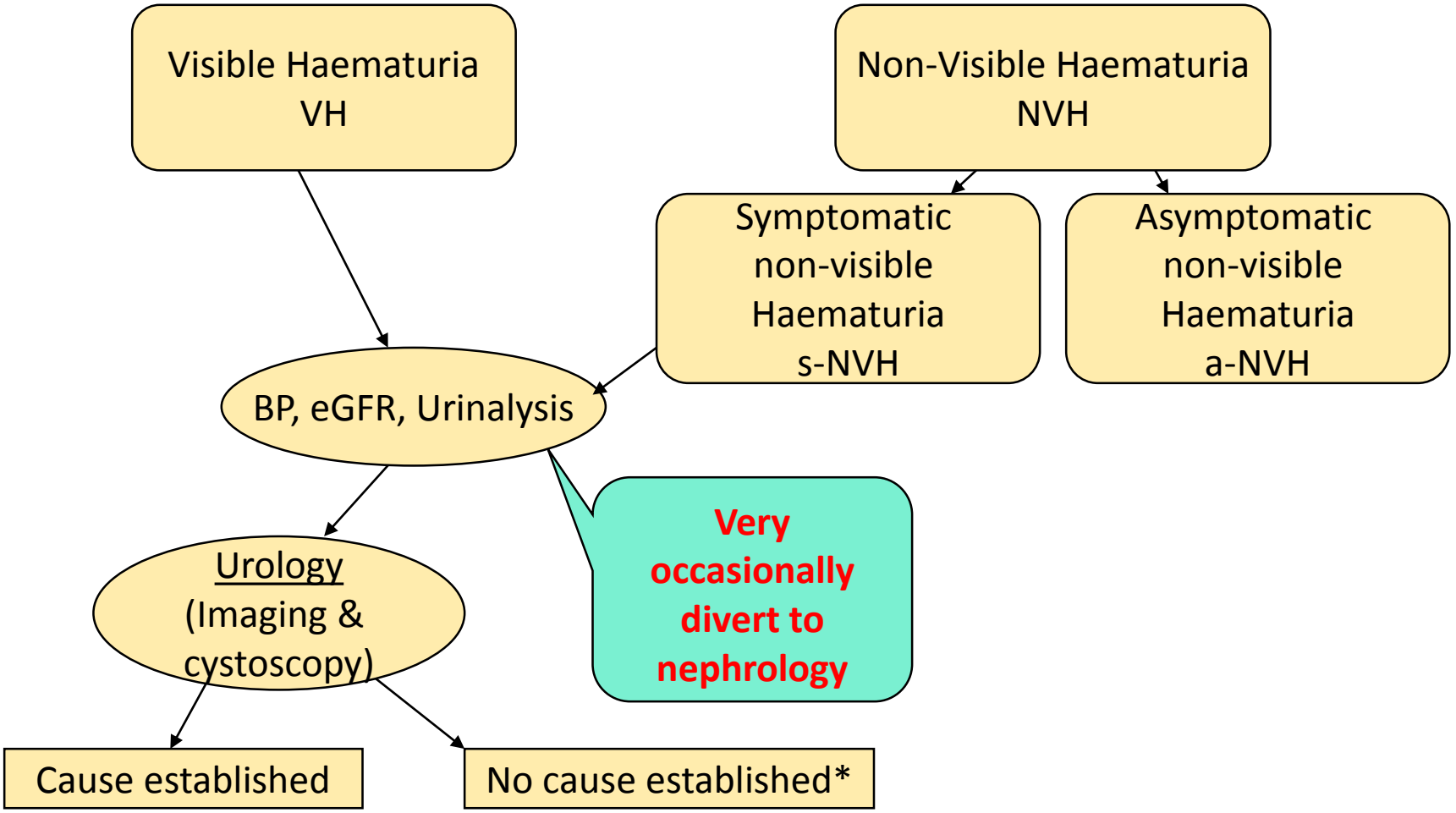
Investigation: VH



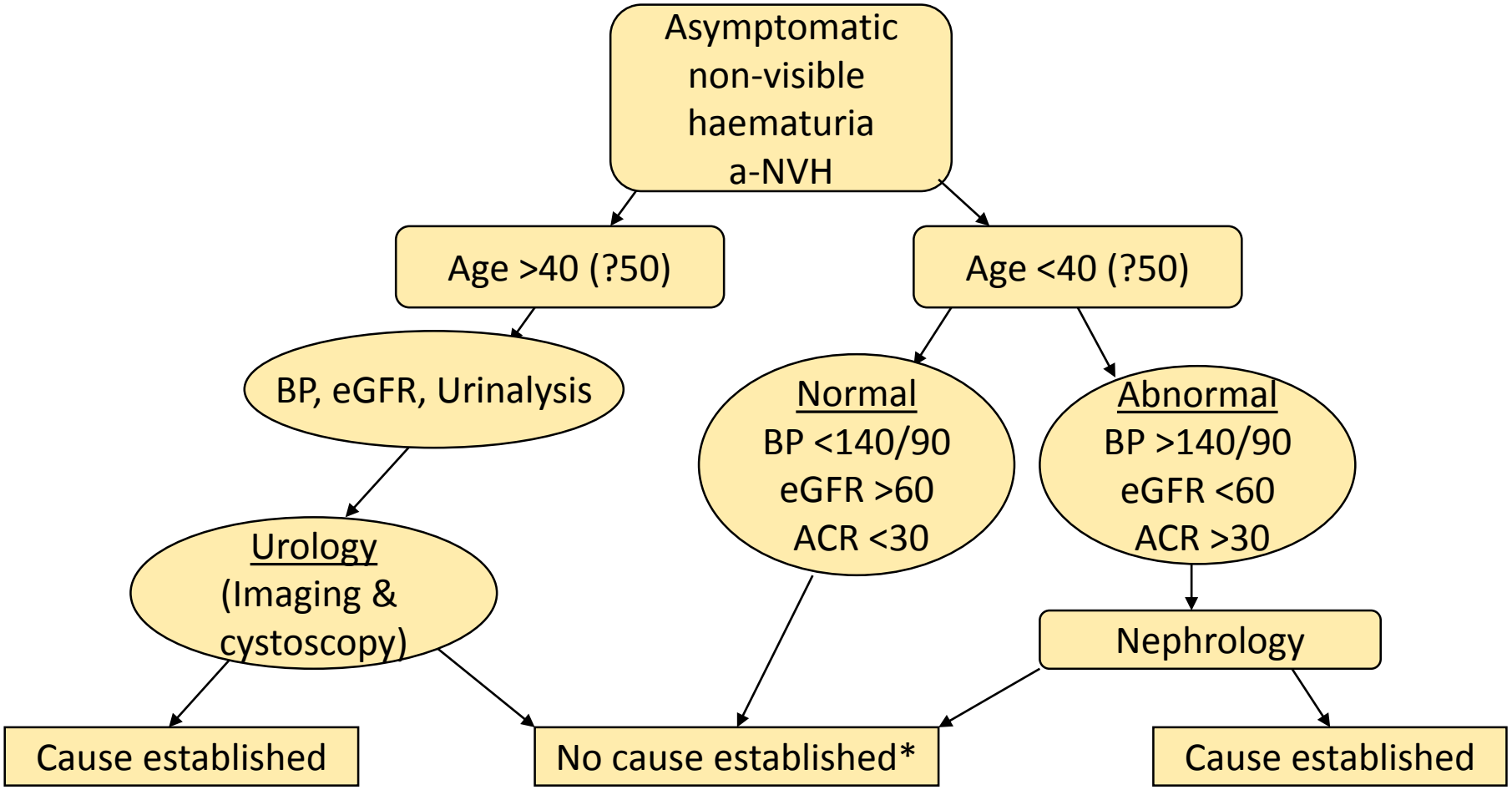
Investigation: s-NVH



Risk of urological malignancy

- Variable risk but increased in: -
  - Smokers
  - Age > 50 male; > 60 female
  - Male > Female
  - History of urological disorder or disease
  - History of storage symptoms / UTI
  - Exposure to benzene / aromatic amines
    - Rubber, textiles, cable, printing
  - Pelvic irradiation

Investigation: a-NVH



Monitoring of Haematuria

No cause established

↓

Primary Care Monitoring

Annual assessment while haematuria persists of BP, eGFR & ACR

Refer or re-refer to urology if:

- Development of VH or s-NVH

Refer to nephrology if:

- Significant or increasing proteinuria (ACR > 30)
- eGFR <30 on 2 readings without an identifiable reversible cause
- Deteriorating eGFR (1 year fall >5ml/min, or >10ml/min in 5 years)

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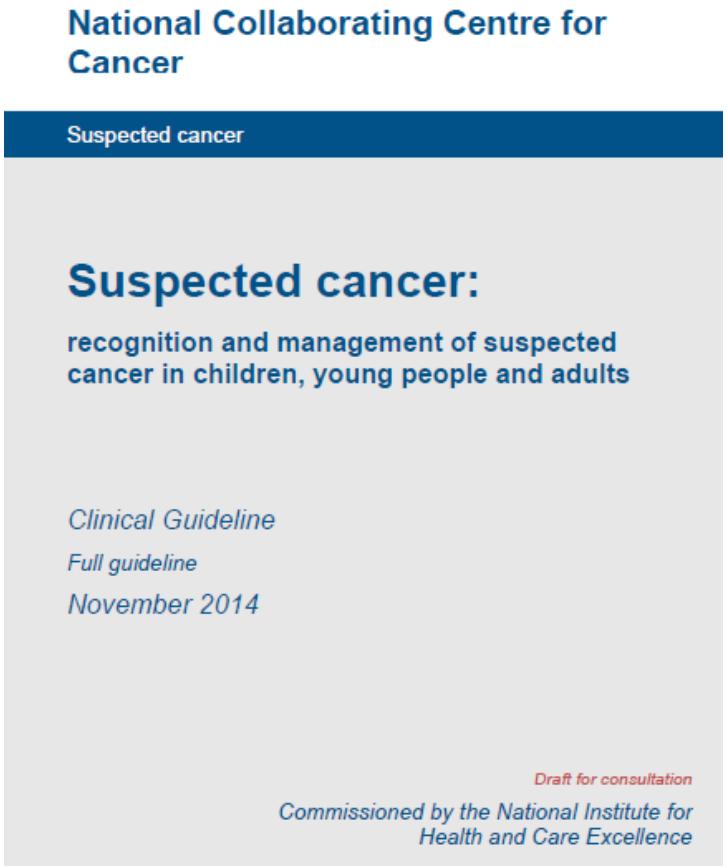
2015



NICE 2015

Bladder cancer

- 10,000 new cases p.a. in UK
- Full time GP diagnoses new case every 3-5 years
- 75% of new cases are male
- 5 yr survival = 55%

Renal cancer

- Over 10,000 new cases p.a. in UK
- Full time GP diagnoses 1 new case every 3-5 years
- 60% of new diagnoses in males
- 5 year survival >55%

NICE 2005 Suspected Cancer CG27

- Patients with painless macroscopic haematuria should be referred urgently at any age
- Patients with symptoms suggestive of UTI with macroscopic haematuria should be referred urgently if infection not confirmed
- Patients 50 years or over with unexplained microscopic haematuria should be referred urgently
- Patients under 50 with normal creatinine and no proteinuria should be referred routinely to a urologist

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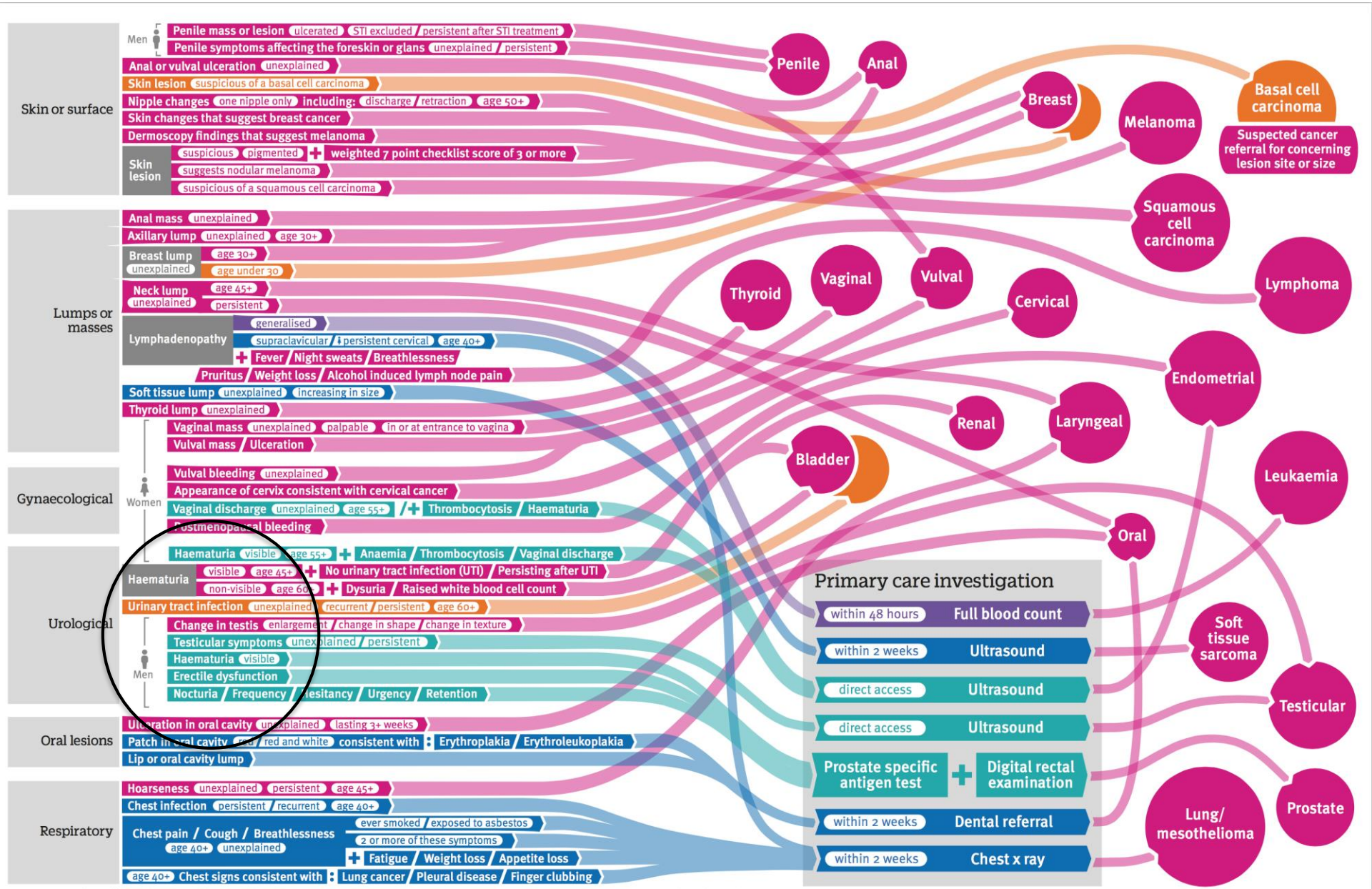

Data source: http://www.bmj.com/content/350/bmj.h3044

Version 3.1. Updated 17 July 2015.

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NICE recommendations 2015

Visible & Unexplained, without UTI or that persists or recurs after successful Rx of UTI, 45 & over

- 2ww ref - ?Bladder / Renal

Non-visible & Unexplained, with dysuria or raised WCC, 60 & over

- 2ww - ?Bladder

Visible with low Hb or thrombocytosis or high blood glucose or unexplained vaginal discharge, women 55 & over

- Direct access pelvic USS - ?Endometrial

Visible, in men

- Consider PSA & DRE - ?Prostate

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Prostate cancer

Urgent referral:
Urgently refer men (appointment within two weeks) if either:

- Their prostate feels malignant on digital rectal examination (DRE)

OR

- Their prostate specific antigen (PSA) levels are above the age-specific reference range.

Non-urgent investigation:
Consider a PSA test **AND** DRE in men with any of the following:

- Any lower urinary tract symptoms, such as nocturia, urinary frequency, hesitancy, urgency or retention
- Erectile dysfunction
- Visible haematuria.

Accompanying notes:
Prostate-specific antigen ranges:

- 40–49 years 0–2.5ng/L
- 50–59 years 0–3.5ng/L
- 60–69 years 0–4.5nh/L
- 70–79 years 0–6.5ng/L

Consider alternative contributing factors that may influence an individual's PSA ranges.

Bladder cancer

Urgent referral:
Urgently refer patients (appointment within two weeks) if they are:

- Aged 45 and over with either:
  - Unexplained visible haematuria without urinary tract infection

  OR
  - Visible haematuria that persists or recurs after successful treatment of urinary tract infection.
- Aged 60 and over with unexplained non-visible haematuria and either:
  - Dysuria

  OR
  - A raised white cell count on a blood test.

Non-urgent referral:
Consider referral in patients aged 60 and over with recurrent or persistent urinary tract infection that is unexplained.

Renal cancer

Urgent referral:
Urgently refer patients (appointment within two weeks) if they are:

- Aged 45 years and over with either:
  - Unexplained visible haematuria without urinary tract infection
  - Visible haematuria that persists or recurs after successful treatment of urinary tract infection.

Testicular cancer

Urgent referral:
Consider urgent referral (appointment within two weeks) in men with any of the following changes in the testis:

- Non-painful enlargement
- Change in shape
- Change in texture.

Direct access ultrasound:
Consider a direct access ultrasound scan in men with unexplained or persistent testicular symptoms.

Penile cancer

Urgent referral:
Consider urgent referral (appointment within two weeks) in men with any of the following, after exclusion of sexually transmitted infection as a cause or after treatment for a sexually transmitted infection has been completed:

- A penile mass
- An ulcerated lesion
- Unexplained **OR** persistent symptoms affecting the foreskin or glans.

Scenario 1

Paul, a 39 year old, is a type 2 diabetic, and found to have non-visible haematuria by your practice nurse. He has had the dipstick repeated 2 weeks after it was initially found and he again had a positive dip result. His last diabetic review was a month ago – his HbA1c is well controlled at 52. He has an eGFR of 50mls/min, an ACR of 45mg/mmol, and a blood pressure of 138/78. His eGFR has deteriorated slightly since the previous result, 12months ago, of 62mls/min.

What would be your next step?

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Scenario 2

Markus, who is 25 years old, has come to see you as part of the morning surgery. He explains that the nurse in the occupational health department at work told him to see his GP as he was found to have non-visible haematuria during a routine medical at work. He has no symptoms, is usually fit and well, and is training for a marathon at present. Markus has not been taking any new medication. His father was diagnosed with ischaemic heart disease aged 52.

What would you do next?

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Scenario 3

Amrita, a 54 year old teacher has been to see the practice nurse for a new-patient appointment and was found to have 3+ blood on a urine dipstick. The nurse comes to discuss her case with you. Amrita has no known medical conditions and is asymptomatic.

What are your next steps?

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Scenario 4

Ben, a 64 year old with well-controlled hypertension comes to see you with LUTS of dysuria and increased daytime frequency. He is an ex-smoker with no relevant family history. You perform a urine dip test which shows Hb2+, leuc 1+.

What will you do now?

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Scenario 5

- Jackie, a 65 year old retail assistant, was seen last week in the haematuria clinic of your local urology department. She had a flexible cystoscopy and renal ultrasound to investigate newly discovered non-visible haematuria. Both investigations were completely normal. She was not told whether she requires any further monitoring and has come to see you to seek advice on this.
- What would you advise?

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