International Journal of Surgery Protocols 21 (2020) 8–12

Contents lists available at ScienceDirect

International Journal of Surgery Protocols

journal homepage: www.elsevier.com/locate/isjp

Protocols

IDENTIFY: The investigation and detection of urological neoplasia in patients referred with suspected urinary tract cancer: A multicentre cohort study

Sinan Khadhouri [a,n], Kevin M Gallagher [b,n], Kenneth MacKenzie [c,n], Taimur T Shah [d,n], Chuanyu Gao [e,n], Sacha Moore [f,n], Eleanor Zimmermann [g,n], Eric Edison [h,n], Matthew Jefferies [i,n], Arjun Nambiar [c,n], Graeme MacLennan [j], John S McGrath [k], Veeru Kasivisvanathan [l,m,n,*], IDENTIFY Protocol Collaborators Group

[a] Aberdeen Royal Infirmary, Dept of Urology, Aberdeen, United Kingdom
[b] Western General Hospital, Dept. of Urology, Edinburgh, United Kingdom
[c] Sunderland Royal Hospital, Dept. of Urology, Sunderland, United Kingdom
[d] Charing Cross Hospital, Imperial College Healthcare NHS Trust, Dept. of Surgery and Cancer, London, United Kingdom
[e] Addenbrookes Hospital, Cambridge, United Kingdom
[f] Wrexham Maelor Hospital, Dept. of Urology, Wrexham, United Kingdom
[g] Torbay and South Devon NHS Foundation Trust, Dept. of Urology, Torbay, United Kingdom
[h] North Middlesex Hospital, Dept. of Urology, London, United Kingdom
[i] Morriston Hospital, Dept. of Urology, Swansea, United Kingdom
[j] University of Aberdeen, Health Services Research Unit, Aberdeen, United Kingdom
[k] University of Exeter Medical School, Dept. of Urology, Exeter, United Kingdom
[l] Division of Surgery and Interventional Science, University College London
[m] University College London Hospitals NHS Foundation Trust, Dept. of Urology, London, United Kingdom
[n] British Urology Researchers in Surgical Training (BURST) Collaborative

1. Background

1.1. Introduction

Globally there are 430,000 new diagnoses of bladder cancer and over 165,000 deaths every year [1]. It is a deadly disease with only 50% of those diagnosed surviving at 10 years [2].

The most common presentation for bladder cancer is haematuria. Patients with suspected bladder cancer are referred to secondary care where a urologist takes focussed history and examination, carries out a cystoscopy [3] and requests imaging, urine and blood tests (Fig. 1). Cystoscopy is the gold standard test used to diagnose bladder cancer. The imaging test is used to assess the upper tracts for malignant (renal or upper tract urothelial cancer) or benign causes of haematuria (e.g. urinary stones) [4].

The bladder cancer rate in patients referred with visible haematuria is 18.9% but only 4.8% in those referred with non-visible haematuria [5]. Upper tract urothelial cancer (UTUC) is rare with an estimated annual incidence of 2 cases per 100,000 inhabitants [2]. Less than 1% of patients referred to secondary care with haematuria have UTUC [6]. A large proportion of patients investigated therefore will have unnecessary, invasive procedures. Cystoscopy causes discomfort and can carry risks such as infection and bleeding and the radiation from a CT scan is associated with secondary malignancy [7]. Equivocal tests can lead to further invasive testing, e.g. biopsy under general anaesthetic, to confirm a negative finding. Annual costs of these investigations are significant. In the UK, patients with normal results from haematuria investigations cost the National Health Service £33.5 million annually [8].

International guidelines for suspected cancer referral pathways vary greatly. Established risk factors are not featured in referral criteria. This may be due to a lack of high-quality evidence. The AUA (American Urological Association) and UK NICE (National Institute for Clinical Excellence) guidelines differentiate between visible and non-visible haematuria, but the evidence behind this is low [9,10]. Both give different age thresholds for recommended investigation of each type of haematuria. These arbitrary thresholds are derived from observation of cancer detection rates for wide age-group categories. In the UK, a National Institute for Health Research (NIHR) Health Technology Assessment systematic review highlighted the uncertainty in the optimal diagnostic pathway for haematuria and specified that future studies should address this [11].

1.2. Rationale

There is currently no published data describing the variation of current diagnostic strategies and respective cancer yield. Some alternative strategies have been proposed, e.g. the use of CT urography as a triage test to avoid performing 17% of flexible cystoscopies [12]. However, a predictive modelling study suggested CT urography in

* Corresponding author at: 3rd Floor, Charles Bell House, 43-45 Foley Street, London W1W 7TS, United Kingdom.
E-mail address: veeru.kasi@ucl.ac.uk (V. Kasivisvanathan).

https://doi.org/10.1016/j.isjp.2020.02.002

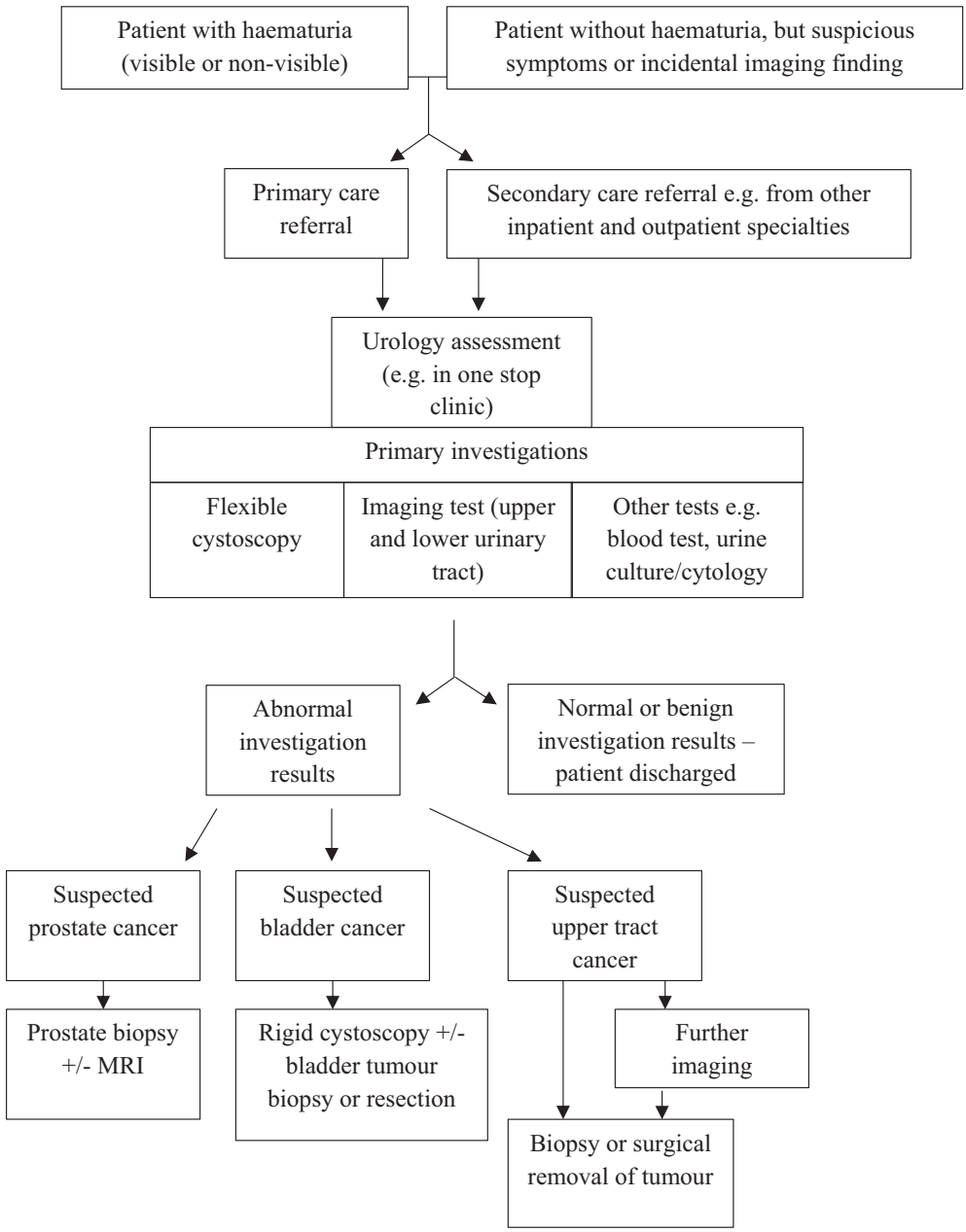

Fig. 1. Typical pathway for a patient referred with suspected urinary tract cancer.

patients with a low risk of urinary tract malignancy may cause more cancers than it diagnoses due to a high radiation dose [13].

Considering the rarity of upper tract cancers, there is a need for a large-scale study in current clinical practice to investigate the optimal strategy for urological cancer diagnosis in patients with haematuria.

IDENTIFY aims to be the largest contemporary study of haematuria investigation. It will provide data on the utility of diagnostic pathways for bladder and upper urinary tract cancer in patients presenting with haematuria, a contemporary evaluation of these pathways and an assessment of the prevalence of urinary tract cancer (bladder cancer, upper tract urothelial cancer, renal cancer and prostate cancer).

We will assess the predictive ability of recognised risk factors for urinary tract cancer and explore novel risk factors that could improve the selection of patients for referral of suspected cancer. By evaluating the patient factors that predict urinary tract cancer and subsequently classifying them in to high, medium and low risk, we will allow clinicians to select the appropriate intensity of investigations. This risk stratification strategy will prompt earlier diagnosis and treatment of more aggressive disease by allocating resources to patients that need them most. It will also optimise use of the most suitable tests to the patient's risk of urothelial cancer. The ultimate hope is that risk stratification will reduce the number of invasive procedures and imaging tests performed, reduce the proportion of negative investigations, and increase cancer diagnostic yield.

Since we do not know the best diagnostic strategies to use and which risk factors are relevant, it was not possible to design an interventional study comparing different strategies. Therefore we designed a prospective observational study with a specifically designed data collection tool.

1.3. IDENTIFY pilot study

The IDENTIFY pilot study collected data on the incidence of urological tract cancer in 824 patients referred with haematuria in 2016, from 7 hospitals in the South of England. It confirmed the feasibility of the project, the processes required to collect data, design of data collection instruments and design of the project management tools for the IDENTIFY study (Appendix A).

2. Methods and analysis

2.1. Study design

The IDENTIFY study is a prospective international multi-centre observational cohort study carried out in urological secondary care centres.

2.2. Aims and objectives

The IDENTIFY study aims to develop risk-based diagnostic strategies for patients referred to secondary care with suspected urinary tract cancer.

Primary Objective: To determine the prevalence of urinary tract cancer in patients referred to secondary care with suspected urinary tract cancer.

The secondary objectives are to determine:

- the prevalence of urinary tract cancers in key clinical subgroups Visible haematuria (VH), Non-visible haematuria (NVH), no haematuria (NH).
- the prevalence of urinary tract cancers by age group and sex.
- current practices in urinary tract cancer diagnosis across different healthcare settings and the effect on prevalence.
- differences in the prevalence of urinary tract cancers in secondary care in different countries.
- risk factors that predict urinary tract cancers and define clinically useful risk stratification groups.
- the diagnostic accuracy of US, CT and urine cytology for bladder, renal and UTUC.
- the diagnostic accuracy of flexible cystoscopy for bladder cancer.
- the cost-effectiveness of different diagnostic strategies for suspected urinary tract cancer

2.3. Study setting

Patient data will be collected from secondary care centres that evaluate patients with suspected urinary tract cancer and have the ability to perform cystoscopy. A list of anticipated participating countries from pre-registered interest in the study can be found in Table 1.

2.4. Eligibility

Patients are included if they are over 16 years of age and were referred to secondary care with haematuria (visible or non-visible), or without haematuria but with suspicious symptoms suggestive of urinary tract cancer.

Exclusion criteria: Patients with a previous or known diagnosis of primary urological cancer, patients referred for suspected recurrence of primary urological cancer, or patients undergoing cystoscopy for a reason unrelated to ruling out urothelial cancer. Patient records lacking sufficient data to determine the primary outcome will be excluded.

Table 1
Anticipated participating countries in the IDENTIFY study.

United Kingdom	France	Netherlands
Argentina	Greece	Poland
Australia	Hong Kong	Portugal
Belgium	Hungary	Singapore
Canada	Iraq	Slovenia
China	Ireland	Spain
Croatia	Italy	Turkey
Czech Republic	Japan	Uruguay
Denmark	Malaysia	USA

2.5. Sample size

The sample size was determined pragmatically based on anticipated accrual. Based on a minimum of 50 patient records collected per site and 100 sites, we plan for a minimum sample size of 5000 patients. Based on the prevalence of urinary tract cancer from the IDENTIFY pilot study of 12%, a confidence level of 95% and a sample size of 5000, the precision for the estimate of urinary tract cancer prevalence will be +/− 0.01%.

2.6. Data collection

Participating collaborators will complete a registration survey describing their normal protocol for the investigation of haematuria at their institution. Data will be collected on consecutive patients seen for assessment, with a minimum of 50 patients per centre. Data collected is routine information recorded as part of clinical assessment. Some patients may undergo further investigations following their initial tests. These can include biopsies, definitive cancer surgery or transurethral resection of bladder tumour (TURBT). This data will also be collected, and patients will be followed up until histopathology is available (if applicable) or until the outcome of their haematuria investigations is complete, whichever is later. It is not anticipated that follow up for any patient will exceed 3 months. Where no cancer is found, patients discharged from secondary care by a urologist will be determined to have met the clinical threshold for a negative cancer outcome.

Non-identifiable patient data will be collected by individual investigators using REDCap electronic data capture tool [14,15].

Data will be collected on:

Hospital protocol (if any) for the investigation of patients with haematuria
Reason for referral
Baseline demographic information
Details of clinical history
Examination findings
Bedside urinalysis
Urine microscopy and cytology results
Blood test results
Ultrasound, CT and other imaging results
Flexible and Rigid cystoscopy results
Histopathology from any biopsies or surgery
Further pathology results within the time frame of the study.

2.7. Quality control

All submitted data will be quality checked by a dedicated independent quality control team. Data will be checked for completion, outliers and adequacy. Queries will be posed to investigators who will have an opportunity to address any deficiencies.

Missing data: All records will be included in the analysis if there is sufficient data to determine the primary outcome. The primary outcome will not be imputed in any case. Missing data will not

be imputed for univariable analysis. Missing data may be imputed in multivariable analysis.

Missing results (tests ordered but not completed) and uninterpretable results (tests performed but inadequate for assessment) will be reported, and reasons examined, but omitted from the main diagnostic test analysis.

2.8. Data analysis plan

We will create a formal statistical analysis plan prior to data analysis.

Prevalence will be calculated as follows:

$$\frac{\text{Total number of patients with target condition}}{\text{Total number of patients at risk}}$$

The defined population at risk are all patients in the study who met the eligibility criteria.

We will also calculate prevalence separately for the following groups:

- Visible haematuria
- Non-visible haematuria
- No haematuria

2.9. Risk factor analysis

We will use multivariate analysis to assess the association of well-established patient risk factors with individual urinary tract cancers. We will also assess less established and controversial risk factors. Together these will be used to develop risk categories for urinary tract cancers.

2.10. Diagnostic test evaluation

Collaborators will score test results on a three-point scale: Normal, Equivocal (defined as a valid test with inconclusive findings) and Positive. Test adequacy will also be recorded [16]. This includes any intended tests that were not performed, tests that were attempted but deemed inadequate, and tests that were completed and were adequate. This will allow for a more accurate diagnostic test evaluation. Sensitivity, specificity, negative and positive predictive values will be reported based on adequately completed tests. Index tests will be compared against specified reference standards for the diagnosis of the relevant cancer type.

2.11. Cost effectiveness

Following analysis of results, diagnostic test strategies will be proposed. The estimated costs of these will be estimated by multiplying standard unit costs by key resource use. Where possible, standard unit costs will be derived from sources such as NHS Reference costs in the UK. A cost analysis will be performed on the various diagnostic strategies proposed. The effect of test inadequacy or equivocal test results will also be taken into account for the cost analysis.

3. Ethics and dissemination

Ethical approval and local regulatory approval will be sought as per local and national guidelines, before commencement of the study. In the UK this study was deemed exempt from ethical approval as per Health Research Authority UK guidance and as per advice from the UK National Research Ethics Service. Each participating UK site will obtain local audit department/Research & Development approval to carry out the study.

Results from the study will be presented in international scientific urological conferences, published in peer-reviewed journals, and submitted to patient advocate groups. It is our intention that all collaborators contributing substantially to the work will have Pubmed indexed collaborator authorship on papers from the study.

4. Guarantor

Sinan Khadhouri and Veeru Kasivisvanathan are the guarantors of this work.

5. Pubmed indexed collaborators

We acknowledge the following individuals who contributed to the peer review of the protocol: Jon Deeks, Mark Emberton, Jeevan Kumaradeevan, Susan Mallet, Steve Morris, Yemisi Takwoingi, Allen Knight, Chris Blick, James Catto, Daniel Cohen, James Green, John Kelly, Hugh Mostafid.

6. Trial registration number

ClinicalTrials.gov NCT03548688.

Author contribution

Protocol writing – Sinan Khadhouri, Kevin Gallagher, Taimur Shah, John McGrath, Veeru Kasivisvanathan

Protocol review and edits – Arjun Nambiar, Matthew Jefferies, Kenneth MackKenzie, Eleanor Zimmermann, Eric Edison, Chuanyu Gao, Sacha Moore, Graeme MacLennan.

Final approval of the version to be published – Sinan Khadhouri, Kevin M Gallagher, Kenneth MacKenzie, Taimur T Shah, Chuanyu Gao, Sacha Moore, Eleanor Zimmermann, Eric Edison, Matthew Jefferies, Arjun Nambiar, Graeme MacLennan, John S McGrath, Veeru Kasivisvanathan.

Ethical approval

In the UK, this project qualifies as a service evaluation as per UK Health Research Authority guidelines and thus there is an exemption from ethical approval requirements. All data is routinely collected, non-identifiable data from routine clinical care. Each participating site will get local audit department/R&D approval to commence work at their site. For international sites, local governance policies will be followed and all required approvals or exemptions will be obtained before commencing the work at the local site.

Funding

Action Bladder Cancer UK, The Rosetree Trust, The Urology Foundation. None had any involvement in the protocol stage of the study.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A

IDENTIFY Pilot study – The Investigation and DEtection of urological Neoplasia in paTIents reFerred with haematuria: A multicentre prospective analYsis.

Khadhouri S, Miller C, Chippagiri A, Moore M, Lobo N, Parsons S, Campain NJ, McGrath JS.

Introduction and objective

This analysis aims to provide an up-to-date overview of haematuria investigations and subsequent urological cancer detection rate. This is in light of recently updated NICE (National Institute for Clinical Excellence) referral guidelines for suspected bladder cancer in June 2015 that aimed to standardise referrals and facilitate early detection of urological cancer.

Methods

Prospective data for 824 patients were collected from 7 hospitals in the south of England for all suspected cancer referrals presenting with haematuria. Those with previous urological malignancy were excluded. Individual hospital protocols for such referrals were also noted.

Results

491 men and 333 women with a median age of 67 were included in the study. 301 (36.5%) patients had non-visible haematuria (NVH); 523 (63.5%) had visible haematuria (VH). All hospitals had cystoscopy and ultrasound (USS) as first line investigations (one hospital used abdominal X-ray alongside USS), and a mixture of CT, intravenous urogram (IVU) and ureterorenoscopy (URS) as second line.

The overall prevalence of urological malignancy was 12.2% (10.4% bladder, 0.6% ureteric/ renal TCC, 1.2% renal); which was 16.4% of the VH group and 5.0% of the NVH group. 85% of malignancies presented with VH. Differences in prevalence existed in sex and age groups. Bladder cancer was found in 5 patients younger than 45 years, 4 of whom presented with VH (an age criteria of 45 or older is recommended in the referral guidelines). A higher percentage of patients with malignancy had a smoking history vs. non-smokers. Stones accounted for 6.7% of presentations.

95.5% of all malignancies and 94.9% of all pathology were diagnosed following an abnormal flexible cystoscopy and/or USS alone. One renal malignancy and 4 upper tract TCCs that were diagnosed with second line investigations had a normal USS.

Conclusions

The prevalence of urological malignancy shown in this analysis compares to previous studies. Second line investigations for upper tract imaging are variable amongst different hospitals. The majority of malignancies were diagnosed following abnormal first line investigations with USS for upper tract imaging. Patients with malignancy were more likely to have a smoking history and present with VH.

References

[1] S. Antoni, J. Ferlay, I. Soerjomataram, A. Znaor, A. Jemal, F. Bray, Bladder cancer incidence and mortality: a global overview and recent trends, Eur. Urol. 71 (2017) 96–108, https://doi.org/10.1016/j.eururo.2016.06.010.
[2] Bladder cancer survival statistics | Cancer Research UK, (n.d.). https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bladder-cancer/survival#heading-Zero (accessed November 19, 2019).
[3] M. Babjuk, A. Böhle, M. Burger, O. Capoun, D. Cohen, E.M. Compérat, V. Hernández, E. Kaasinen, J. Palou, M. Rouprêt, B.W.G. van Rhijn, S.F. Shariat, V. Soukup, R.J. Sylvester, R. Zigeuner, EAU guidelines on non–muscle-invasive urothelial carcinoma of the bladder: Update, Eur. Urol. 71 (2017) (2016) 447–461, https://doi.org/10.1016/j.eururo.2016.05.041.
[4] S.S. Chang, S.A. Boorjian, R. Chou, P.E. Clark, S. Daneshmand, B.R. Konety, R. Pruthi, D.Z. Quale, C.R. Ritch, J.D. Seigne, E.C. Skinner, N.D. Smith, J.M. McKiernan, Diagnosis and treatment of non-muscle invasive bladder cancer: AUA/SUO guideline, J. Urol. 196 (2016) 1021–1029, https://doi.org/10.1016/j.juro.2016.06.049.
[5] T.J. Edwards, A.J. Dickinson, S. Natale, J. Gosling, J.S. McGrath, A prospective analysis of the diagnostic yield resulting from the attendance of 4020 patients at a protocol-driven haematuria clinic, BJU Int. 97 (2006) 301–305, https://doi.org/10.1111/j.1464-410X.2006.05976.x.
[6] M.H. Khadra, R.S. Pickard, M. Charlton, P.H. Powell, D.E. Neal, A prospective analysis of 1,930 patients with hematuria to evaluate current diagnostic practice, J. Urol. 163 (2000) 524–527, https://doi.org/10.1016/S0022-5347(05)67916-5.
[7] T. Yecies, J. Bandari, M. Fam, L. Macleod, B. Jacobs, B. Davies, Risk of radiation from computerized tomography urography in the evaluation of asymptomatic microscopic hematuria, J. Urol. 200 (2018) 967–972, https://doi.org/10.1016/j.juro.2018.05.118.
[8] W.D. Wheelan P, M. Taylor, Economic burden of bladder cancer in the UK, BJU Int. 101 (35) (2008), https://doi.org/10.1111/j.1464-410X.2008.07685.x.
[9] Suspected cancer: recognition and referral | NICE Guidance [NG12], NICE, London, 2015. https://www.nice.org.uk/guidance/ng12 (accessed September 3, 2019).
[10] R. Davis, J.S. Jones, D.A. Barocas, E.P. Castle, E.K. Lang, R.J. Leveillee, E.M. Messing, S.D. Miller, A.C. Peterson, T.M.T. Turk, W. Weitzel, Diagnosis, evaluation and follow-up of asymptomatic microhematuria (AMH) in adults: AUA guideline, J. Urol. 188 (2012) 2473–2481, https://doi.org/10.1016/j.juro.2012.09.078.
[11] M.A. Rodgers, S. Hempel, T. Aho, J.D. Kelly, J. Kleijnen, M. Westwood, Diagnostic tests used in the investigation of adult haematuria: A systematic review, BJU Int. 98 (2006) 1154–1160, https://doi.org/10.1111/j.1464-410X.2006.06406.x.
[12] C.G.T. Blick, S.A. Nazir, S. Mallett, B.W. Turney, N.N. Onwu, I.S.D. Roberts, J.P. Crew, N.C. Cowan, Evaluation of diagnostic strategies for bladder cancer using computed tomography (CT) urography, flexible cystoscopy and voided urine cytology: Results for 778 patients from a hospital haematuria clinic, BJU Int. 110 (2012) 84–94, https://doi.org/10.1111/j.1464-410X.2011.10664.x.
[13] M.V. Georgieva, S.B. Wheeler, D. Erim, R. Smith-Bindman, R. Loo, C. Ng, T. Garg, M. Raynor, M.E. Nielsen, Comparison of the Harms, advantages, and costs associated with alternative guidelines for the evaluation of hematuria, JAMA Intern. Med. (2019), https://doi.org/10.1001/jamainternmed.2019.2280.
[14] P.A. Harris, R. Taylor, B.L. Minor, V. Elliott, M. Fernandez, L. O'Neal, L. McLeod, G. Delacqua, F. Delacqua, J. Kirby, S.N. Duda, REDCap Consortium, The REDCap consortium: Building an international community of software platform partners, J. Biomed. Inform. 95 (2019), https://doi.org/10.1016/j.jbi.2019.103208 103208.
[15] P.A. Harris, R. Taylor, R. Thielke, J. Payne, N. Gonzalez, J.G. Conde, Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support, J. Biomed. Inform. 42 (2009) 377–381, https://doi.org/10.1016/j.jbi.2008.08.010.
[16] B. Shinkins, M. Thompson, S. Mallett, R. Perera, Diagnostic accuracy studies: how to report and analyse inconclusive test results, BMJ 346 (2013) 1–11, https://doi.org/10.1136/bmj.f2778.