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Scottish Referral Guidelines for Suspected Cancer Update – Evidence Review for Bladder and Kidney cancer

The purpose of this document is to synthesise and critique evidence and insight related to referral guidelines for suspected bladder and kidney cancer. Key themes have been determined from the literature. For each key theme e.g. individual symptoms, the papers are summarised separately with some high-level synthesis to provide steer on how this may impact referral guidelines. At the end of the document, a table comparing NICE NG12 and SRG guidelines can be found for reference. Please note that for the purposes of this review, kidney cancer and renal cancer are treated as equivalents.

This document includes evidence on the following topics:

- Individual symptoms
- Symptom combinations
- Investigation findings
- Inequalities in timely diagnosis
- Other considerations for risk of cancer
- Emerging topics
- Other insights

Background (on cancer site)

Bladder cancer is the 13th most common cancer in Scotland, accounting for 2% of all new cancer cases[1] while kidney cancer is the 8th most common cancer in Scotland, accounting for 3% of all new cancer cases.[2] Stage at diagnosis data are not publicly available for either of these cancers in Scotland. In Wales (2019), among the 468 bladder cancer cases with a recorded stage, 45.3% were diagnosed at stage 1, 28.8% at stage 2, 12.6% at stage 3 and 13.2% at stage 4.[3] For kidney cancer in Wales (2019), among 521 cases with a recorded stage, 45.9% were diagnosed at stage 1, 8.3% at stage 2, 20.9% at stage 3, and 25% at stage 4.[2]

[1] 2018+2019+2021
[2] https://www.opendata.nhs.scot/dataset/annual-cancer-incidence
[3] https://crukcancerintelligence.shinyapps.io/EarlyDiagnosis/

Advanced stage at diagnosis is associated with limited treatment options and lower survival. Scotland survival data is unavailable, however, in Wales, 94.0% of those diagnosed with bladder cancer between 2016-2020 at stage 1 survived their disease for one year or more, compared to 23.7% diagnosed at stage 4.[2] For kidney cancer, in Wales 91.6% of those diagnosed with bladder cancer between 2016-2020 at stage 1 survived their disease for five years or more, compared to 13.7% diagnosed at stage 4.[2]

Being diagnosed via emergency presentation is associated with later stage at diagnosis, and poorer outcomes. Scotland routes to diagnosis data is not publicly available for bladder or kidney cancer. In England (2018), among 8,514 bladder cancer cases with a known route to diagnosis, 17.5% were diagnosed via emergency presentation, and among 9,086 kidney cancer cases with a known route to diagnosis, 20.9% were diagnosed via emergency presentation.[2]

The most common symptom of both bladder and kidney cancer is haematuria. Kidney cancer is also associated with more non-specific symptoms, and symptoms usually present when the disease is more advanced. Urinary tract infection (UTI) or symptoms that mimic UTI (i.e., dysuria, urinary frequency, urinary urgency, etc.) are associated with bladder and kidney cancers, which can make timely recognition and referral more challenging for primary care physicians. For bladder cancer, gender inequalities in timely diagnosis exist, with women more likely to experience delays in diagnosis. Women are also more likely to be diagnosed with late-stage bladder cancer. This could be attributed to the tendency for women to present with UTI more frequently than men. Neither of these cancers have recommended screening programmes, which means that improving primary care recognition and referral is vital to improving outcomes.

Search Strategy

Search terms: PubMed search for combinations of the following terms:
"Bladder cancer", "urothelial cancer", "kidney cancer", "renal cancer", "renal cell carcinoma", urological, symptom, symptom*, haematuria, urine, UTI, "urinary tract infection", urinary, urgency, dysuria, frequency, "abdominal pain", "flank pain", "loin pain", fatigue, "weight loss", "abdominal symptom", "lower urinary tract", "urinary tract", diagnosis, detection, risk, prevalence, "positive predictive value", "non-specific symptom", investigat*, test*, "urine test", urinalysis, "urine analysis", dipstick, ultrasound, "urine cytology", "direct access", "primary care", "general practice", inequalt*, gender, women, disparit*, timely, "risk strat*"

Date: 2015 – present. In the table summaries, the only papers included from pre-2015 are those that are relevant for explaining differences in Scottish Referral Guidelines (SRG) and NICE NG12 guidelines. These have been gathered from NICE NG12 Evidence Review document.

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Peer-reviewed literature

Note: grey rows in the table represent studies that have already been summarised earlier in the document.

Topic: Individual symptoms				
Summary: • The overall evidence on symptoms of bladder and kidney cancer supports the inclusion of visible and non-visible haematuria in the absence of UTI, or that persists/recurs after UTI treatment, within the Scottish Referral Guidelines (SRG). • Evidence for the inclusion of abdominal mass in SRG is more limited, as no study evaluated the PPV of abdominal mass and the overall prevalences for abdominal mass reported across the studies was low. • The quality of studies was generally good and used large primary care datasets, however, there was a lack of studies that quantified the positive predictive value (PPV) of symptoms. Most of the studies were conducted in England, and some of the studies recruited patients from secondary care. Additionally, it was unclear in some papers whether haematuria was visible or non-visible, or unspecified. • The systematic review (Paper 6) demonstrated that visible haematuria has the highest PPV for bladder and kidney cancer (~5.1). Haematuria was also the most common symptom of bladder and kidney cancer. Around 50% of people diagnosed with bladder cancer experience haematuria, while only around 15-20% of people diagnosed with kidney cancer experience haematuria. • For bladder cancer, UTI and symptoms that mimic UTI are common. Evidence suggests that UTIs in primary care are often treated presumptively because urine cultures take a few days to come back. However, it is important to consider bladder cancer in these cases, especially if symptoms persist, as studies show that UTIs/UTI-like symptoms are commonly experienced by those diagnosed with kidney/bladder cancer. Notably, evidence on the prevalence/PPV of recurrent UTI is lacking. Lower urinary tract symptoms (LUTS), abdominal pain, fatigue, and weight loss are also prevalent in those diagnosed with bladder cancer although PPVs for these symptoms are all <1%. • For kidney cancer, associated symptoms were more non-specific than in bladder cancer. They include abdominal pain, back pain, fatigue, weight loss, loss of appetite, UTI, or LUTS, all of which have PPVs <1%. Of note, paper 2 found that many people diagnosed with kidney cancer experience no symptoms at all.			
Paper number	Study	Cancer site	Summary	Notes
Bladder *and* Kidney				
1	Koo MM, Swann R, McPhail S, et al. Presenting symptoms of cancer and stage at	Bladder and kidney	This paper examined associations between common presenting symptoms of cancer and stage at diagnosis. There has been debate around whether symptoms present at an	• Cross-sectional population-based study

	diagnosis: evidence from a cross-sectional, population-based study. Lancet Oncol. 2020;21(1):73-79. doi:10.1016/S1470-2045(19)30595-9		early enough stage for there to be possibility for meaningful clinical intervention.
			
			Bladder cancer:
			• The most common symptom of bladder cancer was **haematuria** (not clear whether it was visible or non-visible).
			• Of those subsequently diagnosed with bladder cancer:
			  ○ 55% presented with **haematuria.**
			  ○ 7% presented with **lower urinary tract symptoms (LUTS).**
			  ○ 4% presented with **lower abdominal pain.**
			  ○ 2% presented with **fatigue.**
			  ○ 2% presented with **weight loss.**
			
			Kidney cancer:
			• The most common symptom of kidney cancer was **haematuria** (not clear whether it was visible or non-visible).
			• Of those diagnosed with kidney cancer:
			  ○ 18% presented with **haematuria**.
			  ○ 10% presented with **general abdominal pain.**
			  ○ 7% presented with **lower abdominal pain.**
			  ○ 6% presented with **fatigue.**
			  ○ 6% presented with **weight loss.**
			  ○ 3% presented with **change in bowel habit.**
			  ○ 2% presented with **LUTS.**
			
			Of those that presented with haematuria in the study, about 66% reported this as their only symptom and of these, 18% were
				• N=7,997, aged 25 or older. Unclear how many of these were those diagnosed with bladder or kidney cancer
				• National Cancer Diagnosis Audit (NCDA) and National Cancer Registration and Analysis Service (NCRAS) data (2014)
				• LUTS included: nocturia, frequency, hesitancy, urgency, retention
				• England only
				• Limitation: recording of symptoms and extraction of information from primary care records might be incomplete or biased
				• Did not report positive predictive values (PPV)

			diagnosed at stage 4 *(note: includes cancers other than bladder and kidney),* indicating that symptoms can present early enough for meaningful clinical intervention.	

2	Zakkak N, Barclay ME, Swann R, et al. The presenting symptom signatures of incident cancer: evidence from the English 2018 National Cancer Diagnosis Audit. Br J Cancer. 2024;130(2):297-307. doi:10.1038/s41416-023-02507-4	Bladder and kidney	This paper examined (1) the frequency of presenting symptoms by cancer site and (2) the frequency of cancer site by presenting symptom.
			
			Bladder cancer:
			• The researchers describe bladder cancer as having a "**narrow symptom signature**" because it primarily presents with one symptom – **haematuria** (the paper does not specify whether this is visible or non-visible)**.**
			• 84.7% of patients diagnosed with bladder cancer presented with at least one recorded symptom.
			• Of those diagnosed with bladder cancer in the study:
			  ○ 53% presented with **haematuria** (the paper does not specify whether this is visible or non-visible).
			  ○ 16% presented with **LUTS**.
			  ○ 11% presented with a **UTI.**
			  ○ 9% presented with **dysuria.**
			  ○ 3% presented with **weight loss.**
			  ○ 3% presented with **lower abdominal pain.**
			  ○ 2% presented with **back pain.**
			  ○ 2% presented with **fatigue.**
			  ○ 12% presented with **no recorded symptoms.**
			
			Kidney cancer:
				• N=55,122 patients; 1,518 bladder cancer and 1,695 kidney cancer patients aged 25 or older
				• NCDA 2018 data, England only
				• LUTS included: nocturia, frequency, hesitancy, urgency, retention.
				• Limitations: case-only analysis so cannot make inferences about PPV; surveys for GPs regarding the presenting symptoms were filled out retrospectively and therefore, could be prone to bias.

			• The researchers note that kidney cancer has a **wide symptom presentation**.
			• 63.9% of patients diagnosed with kidney cancer presented with at least one recorded symptom.
			• Of those diagnosed with kidney cancer in the study:
			  ○ 30% presented with **no recorded symptoms.**
			  ○ 15% presented with **haematuria** (the paper does not specify whether this is visible or non-visible)**.**
			  ○ 7% presented with **abdominal pain.**
			  ○ 5% presented with **LUTS.**
			  ○ 5% presented with **back pain.**
			  ○ 4% presented with **loin pain.**
			  ○ 4% presented with **upper abdominal pain.**
			  ○ 4% presented with **fatigue.**
			  ○ 3% presented with a **UTI.**
			  ○ 3% presented with a **cough.**
			  ○ 3% presented with **lower abdominal pain.**
			  ○ 2% presented with **loss of appetite**.
			  ○ 2% presented with **nausea/vomiting**.
			  ○ 2% presented with **dysuria.**
			  ○ 2% presented with **change in bowel habits.**
			  ○ 2% presented with **distension**.
			  ○ 2% presented with **chest pain.**
			
			Note: These symptoms could have occurred individually or in combination with other symptoms	

3	Moore SF, Price SJ, Bostock J, Neal RD, Hamilton W. Incidence of 'Low-Risk but Not	Bladder and kidney	This study explored whether patients who saw their GP with a high-risk cancer symptom had also seen their GP with a 'low-	• Observational, descriptive, cross-sectional study

	No-Risk' Features of Cancer Prior to High-Risk Feature Occurrence: An Observational Cohort Study in Primary Care. Cancers (Basel). 2023;15(15):3936. Published 2023 Aug 2. doi:10.3390/cancers15153936		risk but not no-risk' symptom in the previous year (defined as having a 1-2.99% risk symptom). **Bladder cancer:** Of the participants that experienced a high-risk symptom (>3% risk – most often **haematuria** – the paper did not specify whether this was visible or non-visible): • 6% experienced a 1-1.99% risk symptom in the preceding year. These symptoms included **dysuria** and **anaemia.** The median time of occurrence for these symptoms was 173 days prior to the high-risk symptom. **Kidney cancer:** Of the participants that experienced a high-risk symptom (>3% risk symptom): • 5.7% experienced a 1-1.99% risk symptom in the preceding year. These symptoms included **deep vein thrombosis (DVT)** and **anaemia.** The median time of occurrence for these symptoms was 105 days prior to the high-risk symptom. These results suggest that low PPV symptoms of kidney and bladder cancer may appear early enough for meaningful clinical intervention and earlier diagnosis.	• Clinical Research Practice Datalink (CPRD) data, England only • N=150,921, unclear how many were diagnosed with kidney/bladder cancer • Included data on patients 40 or older from 1 January 2015 to 31 December 2016
4	Zhou Y, Lyratzopoulos G, Rajan P, Walter FM, Wu J. Understanding symptom contribution to sex inequality in bladder and renal cancer	Bladder and kidney	This study aimed to examine the associations between common symptoms of bladder/kidney cancer and stage at diagnosis, with focus on exploring sex differences in stage at diagnosis (the latter is summarised in the 'inequalities' table below).	• CPRD GOLD data linked with other national datasets • N=1151 bladder cancer patients

	stage at diagnosis. BJUI Compass. 2024.		**Bladder cancer:** Of those diagnosed with bladder cancer: • 43.9% experienced **haematuria**. Of these, 91% were diagnosed at an early stage. The paper did not distinguish between visible and non-visible haematuria. • 16.3% experienced **UTI** of which 80% were diagnosed at an early stage. • 14.8% experienced **abdominal symptoms** (including **abdominal pain, loin pain**, **and bowel symptoms)** of which 81% were diagnosed at an early stage. • 3.8% experienced **non-specific symptoms** such as **weight loss, loss of appetite, fatigue, weakness**, and **leg swelling**. Of these, 80% were diagnosed at an early stage. • 12.2% experienced **hypertension**, of which 89% were diagnosed at an early stage. • 2.5% experienced **urinary symptoms** such as **nocturia, poor urinary stream, urinary incontinence,** and **retention.** Of these, 90% were diagnosed at an early stage. **Kidney cancer:** Of those diagnosed with kidney cancer: • 19.3% experienced **haematuria** of which only 40% were diagnosed at an early stage. The paper did not distinguish between visible and non-visible haematuria.	• N=440 renal cancer patients • Limitations: limitations of CPRD data, symptoms may have occurred even before 1 year prior to diagnosis, small sample of people diagnosed with kidney cancer

			• 9.1% experienced **UTI** of which 53% were diagnosed at an early stage. • 32% experienced **abdominal symptoms** (including **abdominal pain, loin pain** , **and bowel symptoms**, of which only 451% were diagnosed at an early stage. • 7.1% experienced **non-specific symptoms** such as **weight loss, loss of appetite, fatigue, weakness**, and **leg swelling.** Of these, only 40% were diagnosed at an early stage. • 4.1% experienced **anaemia** of which only 28% were diagnosed at an early stage. • 17% experienced **hypertension** of which 52% were diagnosed at an early stage. • 3.4% experienced other **urinary symptoms** such as **nocturia, poor urinary stream, urinary incontinence**, and **retention.** Of these, 53% were diagnosed at an early stage.	
5	Zhou Y, Walter FM, Singh H, Hamilton W, Abel GA, Lyratzopoulos G. Prolonged Diagnostic Intervals as Marker of Missed Diagnostic Opportunities in Bladder and Kidney Cancer Patients with Alarm Features: A Longitudinal Linked Data Study. Cancers (Basel). 2021;13(1):156. Published 2021 Jan 5. doi:10.3390/cancers13010156	Bladder and kidney	This paper looked at prevalence of clinical features and diagnostic timeliness among patients diagnosed with bladder and kidney cancer. **Bladder cancer:** Of the 3,397 bladder cancer patients, 44.7% experienced one symptom. • 61.2% experienced **haematuria (visible, non-visible, or unspecified).** • 30.6% experienced **UTI, dysuria, urinary frequency, urinary urgency**, or **malodourous urine** (these symptoms were lumped together).	• Longitudinal linked data study • CPRD data linked with cancer registry, England only • Patients ≥ 25 years old diagnosed with bladder or kidney cancer between April 2012-December 2015 • N=3397 bladder cancer patients; N=1714 kidney cancer patients

			• 8.6% experienced **abdominal pain.** • 7.6% experienced **low back pain.** • 2.9% experienced **fatigue.** • 2.7% experienced **kidney stone/loin pain.** • 2.6% experienced **nocturia.** • 2.2% experienced **urinary retention**. • 2.1% experienced **weight loss**. • 2.0% experienced **anaemia.** • 1.7% experienced **urinary incontinence.** • 1.6% experienced **pelvic pain.** Of note, 22.2% had **no recorded symptoms.** **Kidney cancer:** Of the 1,714 kidney cancer patients included, 37.2% experienced one symptom. • 16.3% experienced **haematuria (visible, non-visible, and unspecified).** • 12.7% experienced **UTI, dysuria, urinary frequency, urinary urgency**, and **malodourous urine** (these symptoms were lumped together). • 13.2% experienced **abdominal pain.** • 9.8% experienced **low back pain.** • 5.6% experienced **kidney stone/loin pain.** • 5.0% experienced **fatigue.** • 3.6% experienced **weight loss.** • 2.9% experienced **anaemia.** • 2.2% experienced **abdominal mass.** • 1.9% experienced **pelvic pain.** • 1.5% experienced **nocturia.**	• *Note that 2005 NICE guidelines CG27 was used to classify patients who met the fast-track referral guidelines • Limitations: CPRD data depends on accurate recording of symptoms by health professionals; often haematuria was recorded as “unspecified” rather than visible or non-visible.

			• 1.5% experienced **urinary retention.** • 1.4% experienced **fever/night sweats.** Of note, 37.9% had **no recorded symptoms.**	
6	Schmidt-Hansen M, Berendse S, Hamilton W. The association between symptoms and bladder or renal tract cancer in primary care: a systematic review. Br J Gen Pract. 2015;65(640):e769-e775. doi:10.3399/bjgp15X687421	Bladder and kidney	This review explored the PPV of symptoms of bladder and renal cancer in primary care. Overall, the only symptom with a PPV >3% was **visible haematuria.** Results from the meta-analysis showed: • A **PPV of 5.1** (95% CI 3.2 to 8.0) **for visible haematuria for bladder or kidney cancer.** • The PPV increased with age in both cancer types. Results from individual studies showed: • The PPV for visible haematuria was higher for bladder cancer than renal cancer. • The PPV reported in individual studies when stratified by sex was often higher for males than females. • The most common non-haematuria symptom was **UTI** (for bladder cancer only) and **abdominal pain** (for both bladder and kidney cancer). • The **PPV** of **non-haematuria symptoms were all below 0.5**, except for **deep vein thrombosis** for kidney cancer which one study reported as being 1.2 (95% CI 0.4 to 2.9) and **anaemia** for bladder and kidney cancer which one study reported as being 1.4 (95% CI 1.1 to 1.9) among males only. • The PPV of non-haematuria symptoms was generally higher for males than females and increased with age.	• Systematic review and meta-analysis (note: the meta-analysis included data on visible haematuria only). • 11 studies included, most conducted in the UK or Europe. • N total=3,451,675 patients • Generally, studies were of moderate to high quality. • Limitations: some studies may not have been fully representative of UK primary care; some studies had missing data or short follow-up.

7	Price SJ, Gibson N, Hamilton WT, King A, Shephard EA. Intra-abdominal cancer risk with abdominal pain: a prospective cohort primary care study. Br J Gen Pract. 2022;72(718):e361-e368. Published 2022 Apr 28. doi:10.3399/BJGP.2021.0552		This study evaluated the risk of kidney and bladder cancers (as well as other cancers) in patients with new abdominal pain with or without haematuria or urinary tract infection. **Bladder cancer** The 1-year incidence of bladder cancer among those that experienced abdominal pain with or without an additional feature, reported by age and sex, is as follows: • **Women aged 40-59:** Incidence 0.01% (95% CI 0.002-0.03). • **Men aged 40-59:** Incidence 0.02% (95% CI 0.01-0.04). • **Women aged 60-69:** Incidence 0.03% (95% CI 0.01 - 0.08) • **Men aged 60-69:** Incidence 0.09% (95% CI 0.05-0.15). • **Women 70+:** Incidence 0.12% (95% CI 0.08-0.17). • **Men 70+:** Incidence 0.25% (95% CI 0.17-0.34) **Kidney cancer** The 1-year incidence of kidney cancer among those that experienced abdominal pain with or without an additional feature, reported by age and sex, is as follows: • **Women aged 40-59:** Incidence 0.01% (95% CI 0.004-0.03) • **Men aged 40-59:** Incidence 0.05% (95% CI 0.03-0.08) • **Women aged 60-69:** Incidence 0.07% (95% CI 0.04-0.13) • **Men aged 60-69:** Incidence 0.08 (95% CI 0.04-0.14). • **Women 70+:** Incidence 0.05% (95% CI 0.02-0.09). • **Men 70+:** Incidence 0.18% (95% CI 0.11-0.27).	• Observational prospective cohort study • CPRD • England only • N=125 793 patients, unclear how many were kidney/bladder cancer patients • Aged ≥40 years • Between 1 January 2009 and 31 December 2013. • Limitations: data is subject to accurate reporting/recording

			Of note, the incidence for both bladder and kidney cancer among those that experienced abdominal pain with or without an additional feature was higher than the age and sex standardised incidence of each cancer in the general population, indicating that those with abdominal pain do have a slightly higher risk of bladder/kidney cancer.	
8	Holtedahl K, Borgquist L, Donker GA, et al. Symptoms and signs of urogenital cancer in primary care. BMC Prim Care. 2023;24(1):107. Published 2023 Apr 26. doi:10.1186/s12875-023-02063-z		This study aimed to analyse non-specific and alarm abdominal symptoms in primary care among a cohort of patients diagnosed with urogenital cancer in 6 European nations. **Macro and micro haematuria** was the most common symptom of both bladder and renal cancer. • The reported **sensitivity** of **macroscopic haematuria** for both cancers combined was 28.3% (17.3–42.6). • The reported **specificity** for **macroscopic haematuria** was 99.8% (99.7–99.8). Additionally, 20% people diagnosed with bladder cancer and 25% of people diagnosed with kidney cancer experienced **abdominal pain.** Non-specific symptoms, including **lack of appetite** and **unusual tiredness**, were experienced only by those diagnosed with kidney cancer. **Note that these findings are severely limited by the small sample size.**	• Data between 25 February 2011 and 27 July 2011 • N=30 Bladder cancer cases and 16 renal • Norway, Denmark, Sweden, the Netherlands, Belgium and Scotland • Limitations: small sample of those with kidney or bladder cancer limits generalisability of findings
Kidney cancer				

9	Vasudev NS, Wilson M, Stewart GD, et al. Challenges of early renal cancer detection: symptom patterns and incidental diagnosis rate in a multicentre prospective UK cohort of patients presenting with suspected renal cancer. BMJ Open. 2020;10(5):e035938. Published 2020 May 11. doi:10.1136/bmjopen-2019-035938	Kidney	This paper evaluated symptoms of kidney cancer and examined their association with early stage disease.
			
			Among the 608 patients diagnosed with kidney cancer in the study, 69% reported symptoms, and of these, 52% reported symptoms that were considered related to the presence of renal cell carcinoma (RCC).
			• 44% had **local symptoms only** (defined as **pain, haematuria, abdominal mass** and/or **other mass**). Specifically:
			  ○ 68% reported **visible haematuria.**
			  ○ 62% reported **pain.**
			  ○ 7% reported an **abdominal mass.**
			• 8.6% had **systemic symptoms only** (defined as **any weight loss, loss of appetite, sweats, fevers, fatigue** and/or **other**). Specifically:
			  ○ 62% reported **fatigue.**
			  ○ 52% reported **weight loss**.
			  ○ 38% reported **sweats.**
			  ○ 38% reported **loss of appetite.**
			  ○ 10% reported **fever**.
			
			Of note, patients with systemic symptoms were more likely to have advanced disease than those with local RCC-related symptoms only. **Visible haematuria** was reported in just 23% of patients, and even in patients with large tumours, haematuria was only reported 47% of the time. Additionally, 60% of cases of kidney cancer in the study were deemed to have been **diagnosed incidentally**, posing a challenge for early diagnosis in primary care.
				• Multicentre prospective observational cohort study
				• Participants recruited between July 2011 and June 2014 from 11 UK centres (8 England, 2 Scotland, 1 Wales)
				• N=706; N=608 diagnosed with kidney cancer during study.
				• Limitations: small sample size; patient-reported symptoms collected after referral to secondary care and could be prone to recall bias.

Topic: Symptom Combinations				
Summary: • Estimates on prevalence of multiple symptoms in those diagnosed with bladder or kidney cancer vary substantially across studies. For example, paper 4 reported prevalences of approximately 3% for experiencing more than one symptom while paper 5 reported prevalences of 25-30%. Paper 9 which focused only on kidney cancer reported that 47.5% of people diagnosed experienced both local and systemic (i.e., non-specific) symptoms. • The PPV of symptoms in combination with haematuria are often high, whereas the PPV of symptom combinations that do not include haematuria are often below 1%, indicating that they are not very good predictors of kidney/bladder cancer. The PPV of symptom combinations also increases with age.				
Paper number	Study	Cancer site	Summary	Notes
Bladder *and* Kidney				
6	Schmidt-Hansen M, Berendse S, Hamilton W. The association between symptoms and bladder or renal tract cancer in primary care: a systematic review. Br J Gen Pract. 2015;65(640):e769-e775. doi:10.3399/bjgp15X687421	Bladder and kidney	This review explored the PPV of symptoms of bladder and renal cancer in primary care. Only four studies reported on symptom combinations, most with small sample sizes so results should be interpreted with caution. In general, the PPV increased significantly for **any symptom when experienced in combination with haematuria.** Additionally, Shephard et al., 2013 reported a PPV of 5% for kidney cancer in males 60+ **with abdominal pain and microcytosis.** However, all other symptom combinations had a PPV of <1%, making them poor predictors for cancer.	• Systematic review and meta-analysis (note: the meta-analysis included data on visible haematuria only). • 11 studies included, most conducted in the UK or Europe; 4 studies reported symptom combinations • N total=3,451,675 patients • Studies on symptom combinations were of lesser quality and smaller sample size.

				• Limitations: some studies may not have been fully representative of UK primary care; some studies had missing data or short follow-up;
7	Price SJ, Gibson N, Hamilton WT, King A, Shephard EA. Intra-abdominal cancer risk with abdominal pain: a prospective cohort primary care study. Br J Gen Pract. 2022;72(718):e361-e368. Published 2022 Apr 28. doi:10.3399/BJGP.2021.0552	Bladder and kidney	This study evaluated the risk of kidney and bladder cancers (as well as other cancers) in patients with new abdominal pain with or without haematuria or urinary tract infection. Results showed that bladder or kidney cancer risk in those with **abdominal pain and haematuria** was: • **Women aged 40-59:** 3.0% (95% CI = 0.6 to 8.5) • **Women aged 60-69:** 2.3% (95% CI =0.3-8.0) • **Women 70+:** 8% (95% CI = 4 to 14) • **Men aged 40-59:** 1.1% (95% CI 0.1-3.9) • **Men aged 60-69:** 1.7% (95% CI = 0.2-5.9) • **Men aged 70+:** 8% (95% CI = 4-12) Bladder or kidney cancer risk in those with **abdominal pain and UTI** was: • **Women aged 40-59:** 0% • **Women aged 60-69:** 0.10% (95% CI = <0.001-0.55) • **Women 70+:** 0.5% (95% CI = 0.3-0.9) • **Men aged 40-59:** 0.9% (95% CI 0.2-2.5) • **Men aged 60-69:** 0% • **Men aged 70+:** 0.2% (95% CI = <0.0-1.1)	• Observational prospective cohort study • CPRD • England only • N=125 793 patients, unclear how many were kidney/bladder cancer patients • Aged ≥40 years • Between 1 January 2009 and 31 December 2013. • Limitations: data is subject to accurate reporting/recording

5	Zhou Y, Walter FM, Singh H, Hamilton W, Abel GA, Lyratzopoulos G. Prolonged Diagnostic Intervals as Marker of Missed Diagnostic Opportunities in Bladder and Kidney Cancer Patients with Alarm Features: A Longitudinal Linked Data Study. Cancers (Basel). 2021;13(1):156. Published 2021 Jan 5. doi:10.3390/cancers13010156	Bladder and kidney	This paper looked at prevalence of clinical features and diagnostic timeliness among patients diagnosed with bladder and kidney cancer. **Bladder cancer:** Of the 3,397 bladder cancer patients, 33.1% experienced two or more symptoms. The symptoms are recorded in the previous table. **Kidney cancer:** Of the 1,714 kidney cancer patients included, 25% experienced two or more symptoms. The symptoms are recorded in the above table.	• Longitudinal linked data study • CPRD data linked with cancer registry, England only • Patients ≥ 25 years old diagnosed with bladder or kidney cancer between April 2012-December 2015 • N=3397 bladder cancer patients; N=1714 kidney cancer patients; • Note that 2005 NICE guidelines CG27 was used to classify patients who met the fast-track referral guidelines • Limitations: CPRD data depends on accurate recording of symptoms by health professionals; often haematuria was recorded as "unspecified" rather than visible or non-visible.
4	Zhou Y, Lyratzopoulos G, Rajan P, Walter FM, Wu J. Understanding symptom contribution to sex inequality in bladder and renal cancer	Bladder and kidney	This study aimed to examine the associations between common symptoms of bladder/kidney cancer and stage at diagnosis, with focus on exploring sex differences in stage at diagnosis (the latter focus is summarised in the 'inequalities' table below).	• CPRD GOLD data linked with other national datasets • N=1151 bladder cancer patients

	stage at diagnosis. BJUI Compass. 2024.		In the study population, 42 (3.6%) bladder cancer and 14 (3.2%) renal cancer patients had more than one symptom at presentation, with the maximum number of presenting symptoms being three (n = 5).	• N=440 renal cancer patients • Limitations: limitations of CPRD data, symptoms may have occurred even before 1 year prior to diagnosis, small sample of people diagnosed with kidney cancer
Kidney cancer				
9	Vasudev NS, Wilson M, Stewart GD, et al. Challenges of early renal cancer detection: symptom patterns and incidental diagnosis rate in a multicentre prospective UK cohort of patients presenting with suspected renal cancer. BMJ Open. 2020;10(5):e035938. Published 2020 May 11. doi:10.1136/bmjopen-2019-035938	Kidney	This paper evaluated symptoms of kidney cancer and examined their association with early-stage disease. 47.5% reported having both local (defined as **pain, haematuria, abdominal mass** and/or **other mass**) and systemic symptoms (defined as **any weight loss, loss of appetite, sweats, fevers, fatigue** and/or **other**).	• Multicentre prospective observational cohort study • Participants recruited between July 2011 and June 2014 from 11 UK centres (8 England, 2 Scotland, 1 Wales) • N=706; N=608 diagnosed with kidney cancer during study. • Limitations: small sample size; patient-reported symptoms collected after referral to secondary care and could be prone to recall bias.

Topic: Investigation findings

Summary:

- Most investigations for bladder and kidney cancer occur in secondary care, however, a primary care professional may request urine, blood, or ultrasound for their patients who present with concerning urological or abdominal symptoms.
- There is a lack of evidence on primary care investigations such as urine or blood tests for bladder and kidney cancer. It's not completely clear what/how many tests are requested in primary care and why. However, the MAINROUTE research team has included some insight that they've derived from analysing primary care data, which we've included in the "other insights" section of this evidence review.
- One study evaluating the diagnostic accuracy of urine cytology for the diagnosis of bladder or urothelial cancer showed poor diagnostic performance. Combining urine cytology with imaging tests such as CT urogram significantly improved sensitivity.

Paper number	Study	Cancer site	Summary	Notes
10	Tan WS, Sarpong R, Khetrapal P, et al. Does urinary cytology have a role in haematuria investigations?. BJU Int. 2019;123(1):74-81. Doi:10.1111/bju.14459	Bladder	This study evaluated the diagnostic accuracy of **urine cytology alone**, and **in combination with other imaging**, to diagnose bladder and upper tract urothelial cancer (UTUC). A positive urine cytology was defined as suspicious/consistent with neoplastic cells, whereas an atypical cytology was classified as showing atyUTI=pical cells. *Note that this paper is an analysis on patients referred to secondary care for haematuria who have enrolled in the DETECT 1 trial, a diagnostic study to assess the performance of an assay to rule out bladder cancer in patients with haematuria.* The **accuracy of a positive/atypical urinary cytology** for the diagnosis of bladder cancer or UTUC was: • **Sensitivity** 43.5%; **Specificity** 95.7% • **PPV** 47.6%; **NPV** 94.9% The diagnostic accuracy of a positive/atypical urinary cytology to identify **high-grade disease** was slightly improved: • **Sensitivity** 57.7%; **Specificity** 94.9%	• Prospective observational study (patients from the DETECT 1 study) • N=567 who underwent urine cytology (n=382 with visible haematuria and n=172 with non-visible haematuria). • Recruitment from 40 UK hospitals for patients referred to secondary care for haematuria • March 2016 and June 2017 • Visible haematuria was defined as haematuria reported by the patient • Non-visible haematuria was defined as a value of

			• **PPV** 35.7%; **NPV** 97.9% Overall, this shows that urinary cytology has a poor diagnostic performance, even for high-grade bladder cancer. The researchers also studied diagnostic performance of urinary cytology combined with upper tract imaging, which significantly increased accuracy. • **Urinary cytology + CT Urogram** had a **sensitivity** of 92.3% and a **specificity** of 94.9% • **Urinary cytology + renal/bladder ultrasonography** had a **sensitivity** of 66.7% and a **specificity** of 96.7% • **CT urogram alone** had a **sensitivity** of 80.5%, **specificity** of 97.0%, **PPV** of 79.3% and **NPV** of 97.2% • **Renal/bladder ultrasonography alone** had a **sensitivity** of 50.7%, a **specificity** of 99.3%, a **PPV** 84.3% and an **NPV** of 96.5% These results suggest that CT urogram may be able to be used as a form of triage to refer patients directly to rigid cystoscopy, however more research is needed.	≥1+ of blood on urine dipstick on ≥2 occasions • Limitations: Difference in methods used for collection and analysis of urine among sites; only a small number (47) of cancers found; lack of long-term follow-up data; patients recruited in secondary care.
11	Tan WS, Sarpong R, Khetrapal P, et al. Can Renal and Bladder Ultrasound Replace Computerized Tomography Urogram in Patients Investigated for Microscopic Hematuria?. J Urol.	Bladder and kidney	This study compared the diagnostic accuracy of CT urogram to renal and bladder ultrasound for identifying urinary tract cancer in patients with microscopic haematuria. *Note that this paper is an analysis on patients referred to secondary care for haematuria who have enrolled in the DETECT 1 trial, a diagnostic study to assess the performance of an assay to rule out bladder cancer in patients with haematuria.*	• Prospective observational study (patients from the DETECT 1 study) • N=3,556 total; N=1,692 who had CT urogram; N=2,166 who had renal bladder ultrasound; n=475 who

	2018;200(5):973-980. Doi:10.1016/j.juro.2018.04.065		**Bladder cancer** The following measures of diagnostic accuracy were reported: • **Renal and bladder ultrasound** had a 50.7% sensitivity, a 99.3% specificity, an 84.3% PPV and a 96.5% NPV. • **CT urogram** had a 80.5% sensitivity, a 97% specificity, a 79.3% PPV, and a 97.2% NPV. The results show that CT urogram has a higher diagnostic accuracy than renal and bladder ultrasound for patients with microscopic haematuria, but still not superior to cystoscopy based on data from other literature in the field. **Kidney cancer** The following measures of diagnostic accuracy were reported: • Renal and bladder ultrasound had a 85.7% sensitivity, a 99.2% specificity, a 41.4% PPV and a 99.9% NPV. • Only the specificity and PPV of CT urogram could be determined. Specificity was 99.9% and PPV was 94.6%. These results show that renal and bladder ultrasound can detect kidney cancer with a high sensitivity for patients with microscopic haematuria although can result in false positive results.	had both CT urogram and renal bladder ultrasound • Recruitment from 40 UK hospitals for patients referred to secondary care for haematuria • March 2016 and June 2017 • Limitations: Investigations were not requested in primary care; variation in scan quality; bladder assessment was limited on some of the scans and these were excluded.

Topic: Inequalities in timely diagnosis
Summary: • Evidence suggests that there are inequalities in timely diagnosis for bladder and kidney cancer. Those with recurrent UTI or symptoms that mimic UTI are more likely to experience delays in diagnosis, perhaps because UTIs are often diagnosed presumptively and may be associated with inadequate clinical examination, repeated antibiotic prescribing without review or referral, and lack of communication of test results.

- Women are also more likely to have a longer primary care interval than men. This could be attributed to the fact that women are more likely to present with recurrent UTI or UTI symptoms. Paper 4 interestingly found that differences in symptom presentation between men and women may explain some of the sex inequality.
- For bladder cancer, those presenting with abdominal symptoms and following an emergency presentation or urgent referral were more likely to have advanced stage disease at diagnosis than those referred routinely.
- For kidney cancer, those diagnosed following emergency presentation were more likely to have advanced stage disease at diagnosis than those referred routinely.
- Prescriptions for UTIs increase approximately 9 months before diagnosis of bladder and kidney cancer and can be up to 11 months before diagnosis in females specifically, which could present an opportunity for earlier intervention. GPs should ensure that patients (especially older women) presenting with recurrent UTI or symptoms similar to UTI are investigated fully and referred if clinical suspicion persists to support timely diagnosis.
- Interestingly, paper 17 found that those aged below the NG12 recommended age threshold (SRG has the same age threshold) with visible haematuria were still at high-risk for intermediate and high-grade cancer. The authors recommend that those with visible haematuria should be investigated fully regardless of age.

Paper number	Study	Cancer site	Summary	Notes
			Bladder *and* Kidney	
12	Zhou Y, Singh H, Hamilton W, et al. Improving the diagnostic process for patients with possible bladder and kidney cancer: a mixed-methods study to identify potential missed diagnostic opportunities. Br J Gen Pract. 2023;73(733):e575-e585. Published 2023 Jul 27. doi:10.3399/BJGP.2022.0602	Bladder and kidney	This study explored missed diagnostic opportunities among patients presenting to primary care with symptoms that could be possible bladder or kidney cancer. This study found that **male patients** presenting with urological/abdominal symptoms that are noted in NG12 as warranting further investigation had higher odds of a cancer referral compared to female patients (adjusted OR 3.03, 95% CI = 2.12 to 4.34, P<0.001). Additionally, patients presenting with **haematuria** compared to those without (adjusted	• Mixed-methods prospective study • June 2018 – Oct 2019 • Patients recruited from 9 GP practices in Eastern England if they presented with eligible urological/abdominal symptoms suggestive of bladder/kidney cancer. • N=940

			OR 2.07, 95% CI = 1.33 to 3.23, P = 0.001) were more likely to receive a cancer referral. *Note: this considers referral for any suspected cancer pathway, not just urological or for bladder/kidney cancer.* Among the patients who presented with **recurrent UTI** eligible for investigation as per NG12, 84.5% (201/238) of them were **women.** Women with recurrent UTI who were referred had a median primary care interval of 35 days compared to 2 days for men who with recurrent UTI who were referred. In general, those who presented with UTI symptoms (especially women) were less likely to receive guideline concordant care, with this study reporting evidence of inadequate clinical examination, repeated antibiotic prescribing without review or referral and a lack of communication of test results. The researchers concluded that women with UTI symptoms are more at risk of missed diagnostic opportunities.	• Limitations: variation in the level of detail and completeness of data collected, missing diagnosis data in 25% of patients, potential over/under estimation of the true odds of referral.
5	Zhou Y, Walter FM, Singh H, Hamilton W, Abel GA, Lyratzopoulos G. Prolonged Diagnostic Intervals as Marker of Missed Diagnostic Opportunities in Bladder and Kidney Cancer Patients with Alarm Features: A Longitudinal Linked Data Study. Cancers (Basel). 2021;13(1):156. Published 2021 Jan 5. doi:10.3390/cancers13010156	Bladder and kidney	This paper looked at prevalence of clinical features and diagnostic timeliness among patients diagnosed with bladder and kidney cancer. Overall, the study found that **patients with recurrent UTIs had the highest odds of having a non-timely diagnosis** (OR 3.46, CI 2.40-5.00; p<0.0001). Symptoms other than visible haematuria were associated with higher odds of non-timely diagnosis	• Longitudinal linked data study • CPRD data linked with cancer registry, England only • Patients ≥ 25 years old diagnosed with bladder or kidney cancer

			as well as female sex (likely due to higher proportions of recurrent UTI in women).	between April 2012-December 2015 • N=3397 bladder cancer patients; N=1714 kidney cancer patients; N=208 upper tract urothelial cancer • Note that 2005 NICE guidelines CG27 was used to classify patients who met the fast-track referral guidelines • Limitations: CPRD data depends on accurate recording of symptoms by health professionals; often haematuria was recorded as "unspecified" rather than visible or non-visible.
4	Zhou Y, Lyratzopoulos G, Rajan P, Walter FM, Wu J. Understanding symptom contribution to sex inequality in bladder and renal cancer stage at diagnosis. BJUI Compass. 2024.	Bladder and kidney	This study aimed to examine the associations between common symptoms of bladder/kidney cancer with focus on exploring sex differences in stage at diagnosis. **Bladder cancer:** The study found the following groups more likely to have advanced-stage diagnoses of bladder cancer:	• CPRD GOLD data linked with other national datasets. • N=1151 bladder cancer patients • N=440 renal cancer patients • Limitations: limitations of CPRD data, symptoms

			• **Women** (OR 1.89, CI 1.29-2.78). Note that the researchers conducted an interaction analysis and found that differences in symptom presentation between men and women may explain some of the sex inequality. • Those diagnosed through **emergency presentation** (OR 7.02, CI 3.93-12.51) compared to routine referral • Those referred through **GP fast-track referral routes** (OR 2.23, CI 1.40-3.55) compared to routine referral • Those **presenting with UTIs** (OR 2.22, CI 1.34-3.69) compared to haematuria (the researchers did not specify whether this was visible or non-visible) • Those **presenting with abdominal symptoms** (OR 2.19, CI 1.30-3.70) compared to haematuria (the researchers did not specify whether this was visible or non-visible) **Kidney cancer:** The only statistically significant association between kidney cancer and advanced stage diagnosis was for those diagnosed following **emergency presentation** (OR 2.62, CI 1.37-5.03) compared to routine referral. The reliability of the findings for kidney cancer may be limited by the small sample size.	may have occurred even before 1 year prior to diagnosis, small sample of people diagnosed with kidney cancer

13	Funston G, Moullet M, Mounce L, Lyratzopoulos G, Walter FM, Zhou Y. Pre-diagnostic prescription patterns in bladder and renal cancer: a longitudinal linked data study. Br J Gen Pract. Published online December 12, 2023. doi:10.3399/BJGP.2023.0122	Bladder and kidney	This study explored relevant prescription patterns in patients up to 2 years prior to diagnosis of bladder and kidney cancer in order to identify potential opportunities for more timely investigation. The researchers only considered prescriptions for medications used to treat symptoms that are similar to those of bladder/kidney cancer. **Bladder cancer:** • In women, 60.6% of prescriptions were for UTI. • In men, 65.2% of prescriptions were for obstructive symptoms (such as hesitancy, poor stream, and urinary retention). • In the year before diagnosis, there was an increase in prescriptions for (1) irritative symptoms (such as dysuria, urinary frequency and urgency) in both sexes, (2) obstructive symptoms (such as hesitancy, poor stream, and urinary retention) in males, and (3) genital infections and atrophic vaginitis in females. **Renal cancer:** • In women, 51.7% of prescriptions were for UTI. • In men, 68.1% of prescriptions were for obstructive symptoms. • In the year before diagnosis, there was an increase in prescriptions for obstructive symptoms in males.	• CPRD GOLD • England only • Diagnosed between April 2012-December 2015 and aged 25 or older • N=3,398 bladder cancer patients • N=1,715 kidney cancer patients • Limitations: limitations of CPRD data, prescribing practices may have changed from 2015 especially due to COVID-19 so results may not be generalisable now, unclear what the exact reason for prescribing medication was.

			For both cancers, the increase from baseline in rate of prescriptions for UTIs occurred approximately 9 months before diagnosis. When examining by gender, females may have an earlier inflection point (~11 months) compared to males (~7 months). This indicates that there may be opportunity to investigate and refer earlier to combat delays in diagnosis, especially for women and in cases of recurrent UTI.	
14	Tan, W. S., Feber, A., Sarpong, R., Khetrapal, P., Rodney, S., Jalil, R., Mostafid, H., Cresswell, J., Hicks, J., Rane, A., Henderson, A., Watson, D., Cherian, J., Williams, N., Brew-Graves, C., Kelly, J. D., & DETECT I trial collaborators (2018). Who Should Be Investigated for Haematuria? Results of a Contemporary Prospective Observational Study of 3556 Patients. European urology, 74(1), 10–14. https://doi.org/10.1016/j.eururo.2018.03.008	Bladder and kidney	This study investigated which demographic groups should be investigated for haematuria, comparing evidence to current NICE guidance which includes age thresholds. *Note that this paper is an analysis on patients referred to secondary care for haematuria who have enrolled in the DETECT 1 trial, a diagnostic study to assess the performance of an assay to rule out bladder cancer in patients with haematuria.* Overall, 602 patients (16.9%) were referred below the NICE recommended age threshold for visible haematuria or non-visible haematuria. The incidence of cancer in patients with visible haematuria <45 years was 3.5% (n=7) and 1.0% (n=4) in patients with non-visible haematuria <60 years. The majority of these cancers were high or intermediate risk cancers.	• Prospective observational study (patients from the DETECT 1 study) • N=3,556 patients • Recruitment from 40 UK hospitals for patients referred to secondary care for haematuria • March 2016 and June 2017 • Visible haematuria was defined as haematuria reported by the patient • Non-visible haematuria was defined as a value of ≥1+ of blood on urine dipstick on ≥2 occasions • Limitations: Patients are from secondary care, so

			The authors recommended that patients presenting with visible haematuria should be investigated for cancer regardless of the age of the individual.	may not be representative of primary care population and detection rates may be higher than if sampled from primary care.

Topic: Other considerations for risk of cancer				
Summary: • Risk of bladder and kidney cancer incidence and mortality is significantly increased among people with a smoking history.[4,5,6] Other risk factors include occupational exposures to chemicals often found in the textile manufacturing industry or any industry that involves combustion.[4,5] • For bladder cancer, risk of advanced stage disease at diagnosis is higher in (1) those younger than 40 and older than 85, (2) women, and (3) people from more deprived areas. • For kidney cancer, risk of advanced stage disease at diagnosis is higher in those over 80 years old and men. There is also various inherited conditions or gene changes which can increase a person's risk of kidney cancer, including Von Hippel-Lindau syndrome, tuberous sclerosis complex, Birt-Hogg-Dubé syndrome, and hereditary papillary renal cell cancer.[7]				
Paper number	Study	Cancer site	Summary	Notes
Bladder *and* Kidney				
15	Barclay, M. E., Abel, G. A., Greenberg, D. C., Rous, B., & Lyratzopoulos, G. (2021). Socio-demographic variation in stage at diagnosis of breast, bladder, colon, endometrial, lung,		This study examined sociodemographic variation in stage at diagnosis for common cancers in England. **Bladder cancer:**	• Cross sectional study • Data from the English cancer registry in 2015

[4] Cumberbatch, M. G., Rota, M., Catto, J. W., & La Vecchia, C. (2016). The Role of Tobacco Smoke in Bladder and Kidney Carcinogenesis: A Comparison of Exposures and Meta-analysis of Incidence and Mortality Risks. European urology, 70(3), 458–466. https://doi.org/10.1016/j.eururo.2015.06.042
[5] Cancer Research UK. Risks and causes of bladder cancer. (2023). Available from: https://www.cancerresearchuk.org/about-cancer/bladder-cancer/risks-causes
[6] Cancer Research UK. Risks and causes of kidney cancer. (2023). Available from: https://www.cancerresearchuk.org/about-cancer/kidney-cancer/risks-causes
[7] Cancer Research UK. Risks and causes of kidney cancer. (2023). Available from: https://www.cancerresearchuk.org/about-cancer/kidney-cancer/risks-causes

	melanoma, prostate, rectal, renal and ovarian cancer in England and its population impact. British journal of cancer, 124(7), 1320–1329.		The following associations between bladder cancer and advanced stage at diagnosis were reported: • Those **younger than 40 and older than 85** had increased odds of advanced stage bladder cancer. • **Women** had a higher risk of advanced stage bladder cancer compared to men. • **More deprived** patients were at higher risk of advanced stage bladder cancer. The researchers estimated that if sociodemographic differences were eliminated, there would be a 5.2% absolute increase in stage I/II diagnoses of bladder cancer. **Kidney cancer:** The following associations between kidney cancer and advanced stage at diagnosis were reported: • **Those over 80 years old** have increased odds of advanced stage kidney cancer. • **Men** had a higher risk of advanced stage at diagnosis compared to women. The researchers estimated that if sociodemographic differences were eliminated, there would be a 6.2% absolute increase in stage 1/11 diagnoses of kidney cancer.	• N=202,001; 8,572 with bladder cancer, 8,933 with renal cancer, 3,103 with renal cell carcinoma • Limitations: stage data missing for some patients; health-care related factors were not considered; • For kidney cancer, the researchers noted substantial morphological heterogeneity, so all kidney cancer models were adjusted for morphology group.

Emerging Topics

Risk prediction

The potential for risk prediction models and risk stratification in primary care is an emerging topic within bladder and kidney cancer to improve recognition. A 2021 systematic review by Harrison H, et al. (2021)[8] identified 29 published models that incorporate clinical signs and symptoms as well as demographics (age, sex, ethnicity), lifestyle factors (smoking, BMI), abnormal blood or urine tests, or urinary biomarkers to predict the risk of bladder or kidney cancer. Most studies were tested on European or North American populations, and most were evaluating bladder cancer, with only one study on kidney cancer prediction. Overall, there were 13 models that demonstrated good discrimination for urological cancer, however only eight had been externally validated. This could be a developing area where models may be able to support primary care professionals to guide referral, but more external validation is required.

Haematuria clinics

One-stop or nurse-led haematuria clinics are present across the UK. Haematuria is a common symptom for bladder and kidney cancer but is also highly prevalent in benign conditions. Timely investigation is required to diagnose cancer earlier, however there is significant pressure on clinical workforce and resources. Therefore, nurse practitioner-led diagnostic services and one-stop rapid clinics for haematuria have been evaluated where nurses may conduct investigations such as flexible cystoscopy.[9] Results show that these clinics provide efficient management of patients and can reduce time from referral to investigation and diagnosis.

Screening

The UK National Screening Committee (UK NSC) does not currently recommend screening for bladder or kidney cancer. However, the ongoing YORKSURe study is assessing urine self-testing kits for haematuria as a way to screen high-risk populations in Leeds, Sheffield and

[8] Harrison H, Usher-Smith JA, Li L, et al. Risk prediction models for symptomatic patients with bladder and kidney cancer: a systematic review. Br J Gen Pract. 2021;72(714):e11-e18. Published 2021 Dec 31. doi:10.3399/BJGP.2021.0319

[9] Madaan A, Kuusk T, Hamdoon M, Elliott A, Pearce D, Madaan S. Nurse-led one stop hematuria clinic: Outcomes from 2,714 patients. BJUI Compass. 2021;2(6):385-394. Published 2021 Jun 12. doi:10.1002/bco2.100

South Yorkshire.[10] Additionally, the Yorkshire Kidney Screening Trial is currently investigating whether an extra CT scan for kidney cancer can be effectively incorporated into targeted lung screening programmes in Leeds.[11]

Biomarkers

There has been emerging research and development into urinary biomarkers, collected through urine samples (also termed 'urine-based liquid biopsy'), that may help to better identify who should receive a cystoscopy.[12,13] Cystoscopy is an invasive and costly test and can have a low sensitivity for early-stage disease, however urinary biomarkers may be able to combat these limitations. There are several that have been commercially created with varying levels of reported sensitivity and specificity. No biomarker is currently recommended for diagnostic use, but research and trials into this space are ongoing.

Suspected Cancer Referral Guidelines: NG12 and SRG

	NG12	SRG

Bladder	Refer people using a suspected cancer pathway referral 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 or
	• aged 60 and over and have unexplained non-visible haematuria and either dysuria or a raised white cell count on a blood test. [2015]
		Bladder and kidney cancer:
		• Aged 45 and over and have unexplained visible haematuria without urinary tract infection
		• Visible haematuria that persists or recurs after successful treatment of urinary tract infection
		• Aged 60 and over and have persistent unexplained non-visible haematuria in the absence of urinary infection
		• Abdominal mass identified clinically or on imaging that is thought to arise from the urinary tract

[10] Yorkshire screening of urine trial (YORKSURe). ISRCTNregistry. Available from: https://www.isrctn.com/ISRCTN34273159
[11] Yorkshire Kidney Screening Trial. Yorkshire Cancer Research. Available from: https://www.yorkshirecancerresearch.org.uk/research-story/yorkshire-kidney-screening-trial
[12] Oliveira MC, Caires HR, Oliveira MJ, Fraga A, Vasconcelos MH, Ribeiro R. Urinary Biomarkers in Bladder Cancer: Where Do We Stand and Potential Role of Extracellular Vesicles. Cancers (Basel). 2020;12(6):1400. Published 2020 May 29. doi:10.3390/cancers12061400
[13] Zeng Y, Wang A, Lv W, et al. Recent development of urinary biomarkers for bladder cancer diagnosis and monitoring. Clin Transl Disc. 2023; 3:e183. https://doi.org/10.1002/ctd2.183

	Consider non-urgent referral for bladder cancer in people aged 60 and over with recurrent or persistent unexplained urinary tract infection. [2015]	
Kidney	Refer people using a suspected cancer pathway referral for renal 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. [2015]	